Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Clinical Packet
May 8, 2024

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Pharmacy and Therapeutics (P&T) Committee
Helpful Hints/Reference Document
P&T Charge

As defined by §22-6-122

The Medicaid Pharmacy and Therapeutics (P&T) Committee shall review and recommend classes of drugs to the Medicaid Commissioner for inclusion in the Medicaid Preferred Drug Plan. Class means a therapeutic group of pharmaceutical agents approved by the FDA as defined by the American Hospital Formulary Service.

The P&T Committee shall develop its preferred drug list recommendations by considering the clinical efficacy, safety and cost effectiveness of a product. Within each covered class, the Committee shall review and recommend drugs to the Medicaid Commissioner for inclusion on a preferred drug list. Medicaid should strive to insure any restriction on pharmaceutical use does not increase overall health care costs to Medicaid.

The recommendations of the P&T Committee regarding any limitations to be imposed on any drug or its use for a specific indication shall be based on sound clinical evidence found in labeling, drug compendia and peer reviewed clinical literature pertaining to use of the drug. Recommendations shall be based upon use in the general population. Medicaid shall make provisions in the prior approval criteria for approval of non-preferred drugs that address needs of sub-populations among Medicaid beneficiaries. The clinical basis for recommendations regarding the PDL shall be made available through a written report that is publicly available. If the recommendation of the P&T Committee is contrary to prevailing clinical evidence found in labeling, drug compendia and/or peer-reviewed literature, such recommendation shall be justified in writing.

Preferred Drug List/Program Definitions

Preferred Drug: Listed on the Agency's Preferred Drug Lists and will not require a prior authorization (PA).

Preferred with Clinical Criteria: Listed on the Agency's Preferred Drug Lists but will require a prior authorization. Clinical criteria must be met in order to be approved.

Non Preferred Drug: Covered by the Agency, if it is determined and supported by medical records to be medically necessary, but will require a PA.

Non Covered Drug: In accordance with Medicaid Drug Amendments contained in the Omnibus Budget Reconciliation Act of 1990 (OBRA 90 federal legislation), the Agency has the option to not cover (or pay for) some drugs. Alabama Medicaid does not cover/pay for the following:

- Drugs used for anorexia, weight loss or weight gain, with the exception of those specified by the Alabama Medicaid Agency
- Drugs used to promote fertility with the exception of those specified by the Alabama Medicaid Agency
- Drugs used for cosmetic purposes or hair growth
- Over-the-counter/non prescription drugs, with the exception of those specified by the Alabama Medicaid Agency
- Covered outpatient drugs when the manufacturer requires as a condition of sale that associated test and/or monitoring services be purchased exclusively from the manufacturer or designee
- DESI (Drug Efficacy Study Implementation [less than effective drugs identified by the FDA]) and IRS (Identical, Related and Similar [drugs removed from the market]) drugs which may be restricted in accordance with Section 1927(d) (2) of the Social Security Act
- Agents when used for the symptomatic relief of cough and colds except for those specified by the Alabama Medicaid Agency
- Prescription vitamin and mineral products, except prenatal vitamins and fluoride preparations and others as specified by the Alabama Medicaid Agency
- Agents when used for the treatment of sexual or erectile dysfunction, unless authorized for pulmonary hypertension.

(From Alabama Medicaid Agency Administrative Code, Chapter 16 and Alabama Medicaid Agency Provider Billing Manual, Chapter 27.)

Prior Authorization (PA): Process that allows drugs that require approval prior to payment to be reimbursed for an individual patient. Drugs may require PA if they are preferred with clinical criteria, are non-preferred status, or if they required PA prior to the PDL.

Medicaid may require prior authorization for generic drugs only in instances when the cost of the generic product is significantly greater than the net cost of the brand product in the same AHFS therapeutic class or when there is a clinical concern regarding safety, overuse or abuse of the product.

Although a product may require PA, the product is considered a covered product and Medicaid will pay for the product only once the PA has been approved.

Override: Process where drugs require approval prior to payment to be reimbursed for an individual patient if the claim falls outside a predetermined limit or criteria. Overrides differ from PA in that drugs or drug classes that require an override will automatically allow payment of the drug unless something on the claim hits a predetermined limit or criteria. The different types of overrides include:

Accumulation Edit
Brand Limit Switchover
Dispense As Written Override
Early Refill
Ingredient Duplication
Maintenance Supply Opt Out
Maximum Unit/Max Cost Limitations
Short Acting Opioid Naïve Override
Therapeutic Duplication

Electronic PA (EPA): The EPA system checks patient-specific claims history to determine if pharmacy and medical PA requirements are met at the Point-of-Sale claim submission for a non-preferred drug. If it is determined that all criteria are met and the request is approved, the claim will pay and no manual PA request will be required. Electronic PA results in a reduction in workload for providers because the claim is electronically approved within a matter of seconds with no manual PA required.

Prior Authorization Criteria Definitions

Appropriate Diagnosis: Diagnosis(es) that justifies the need for the drug requested. Diagnosis(es) **or** ICD-10 code(s) may be used. Use of ICD-10 codes provides specificity and legibility and will usually expedite review.

Prior Treatment Trials: Prior authorization requires that two (2) prescribed generic, OTC or brand name drugs have been utilized unsuccessfully relative to efficacy and/or safety within six (6) months prior to requesting the PA. The PA request must indicate that two (2) generic, OTC or other brand drugs have been utilized for a period of at least thirty (30) days each (14 days for Triptans, 3 days for EENT Vasoconstrictor Agents), **unless** there is an adverse/allergic response or contraindication. If the prescribing practitioner feels there is a medical reason for which the patient should not be on a generic, OTC or brand drug or drug trial, medical justification may be submitted in lieu of previous drug therapy. One prior therapy is acceptable in those instances when a class has only one preferred agent, either generic, OTC, or brand.

Stable Therapy: Allows for approval of a PA for patients who have been determined to be stable on a medication (same drug, same strength) for a specified timeframe and who continue to require therapy. Medications paid for through insurance, private pay or Medicaid are also counted toward the requirement. Providers will be required to document this information on the PA request form and note the program or method through which the medication was dispensed.

Medical Justification: An explanation of the reason the drug is required and any additional information necessary. Medical justification is documentation to support the physician's choice of the requested course of treatment. Documentation from the patient record (history and physical, tests, past or current medication/treatments, patient's response to treatment, etc) illustrates and supports the physician's request for the drug specified. For example, if a recommended therapy trial is contraindicated by the patient's condition or a history of allergy to a first-line drug, and the physician wants to order a non-preferred drug, documentation from the patient record would support that decision. In addition, medical justification may include peer reviewed literature to support the use of a non-preferred medication.

External Criteria

Antihypertensive Agents

Appropriate Diagnosis

- The patient must have an appropriate diagnosis supported by documentation in the patient record.

Prior Treatment Trials

- The patient must also have failed 30-day treatment trials with at least two prescribed and preferred antihypertensive agents in this class, either generic, OTC, or brand, within the past 6 months or have a documented allergy or contraindication to all preferred agents in this class.

- To meet these prior usage requirements, drugs within this specific classification must be judged against others in the same class (AHFS specific). For example, to qualify for a non-preferred beta-blocker, the patient must have met prior usage requirements of 30-day treatment trials with two other preferred beta-blockers, either generic, OTC, or brand.

- For fixed-dose combination products containing drugs from 2 or more different subclasses, prior therapies must include at least 2 prescribed and preferred agents from the respective subclasses.

- For BiDil®, in lieu of prior usage requirements, approval may be obtained for adjunctive therapy to standard heart failure therapy (including a diuretic, angiotensin converting enzyme inhibitor or angiotensin II receptor antagonist, and beta-blocker) in self-identified black patients.

- For Hemangeol®, patients must be five weeks to five months of age when initiating treatment. Hemangeol® may only be approved for the treatment of proliferating infantile hemangioma requiring systemic therapy.

- For Jynarque®, patients must have documented ALT, AST and bilirubin values before initiating treatment. Jynarque® may only be approved to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease.

- For Samsca®, patients must have a documented serum sodium <125 mEq/L, or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction. Patients must also have documentation of being initiated on Samsca® in an inpatient setting.

Stable Therapy

- Approval may be given for those who have documented stable therapy on the requested medication for 60 consecutive days or greater.

Medical Justification

- Medical justification may include peer reviewed literature, medical record documentation, or other information specifically requested.

PA Approval Timeframes

- Approval may be given for up to 12 months.

Electronic Prior Authorization (EPA)

- Antihypertensive agents are included in the electronic PA program.

Verbal PA Requests

- Not Applicable

Alzheimer's Agents

Appropriate Diagnosis

- The patient must have an appropriate diagnosis supported by documentation in the patient record.

- For Aduhelm® (aducanumab-avwa) and Leqembi® (lecanemab-irmb), the diagnosis must be for mild cognitive impairment (MCI) or mild dementia associated with Alzheimer's Disease and all of the criteria as outlined in Alzheimer's Agents Attachment A must be met.

Prior Treatment Trials

- The patient must also have failed 30-day treatment trials with at least one other prescribed and preferred Alzheimer's agent in this class, either generic, OTC, or brand, within the past 6 months, or have a documented allergy or contraindication to all preferred agents in this class.

Stable Therapy

- Stable therapy for this class is defined as a 90-day or greater timeframe. Approval may be given for those who have documented stable therapy on the requested medication for 90 consecutive days or greater.

Medical Justification

- Medical justification may include peer-reviewed literature, medical record documentation, or other information specifically requested.

PA Approval Timeframes

- Approval for Aduhelm® (aducanumab-avwa) may be given for up to 6 months with a follow-up MRI required prior to the 5th, 7th, 9th, and 12th infusions. Approval for Leqembi® (lecanemab-irmb) may be given for up to 6 months with a follow-up MRI required prior to the 5th, 7th, and 14th infusions. Evidence of the patient NOT having disease progression and documentation of ARIA monitoring is required.

- Approval for other agents may be given for up to 12 months.

Verbal PA Requests

- PA requests that meet prior usage requirement for approval may be accepted verbally.

AGENDA
ALABAMA MEDICAID AGENCY
PHARMACY AND THERAPEUTICS (P&T) COMMITTEE

May 8, 2024
1:00 p.m. – 3:00 p.m.

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1. Opening remarks…….Chair
2. Approval of February 7, 2024 P&T Committee Meeting minutes……...…….Chair
3. Pharmacy program update.....Alabama Medicaid
4. Oral presentations by manufacturers/manufacturers' representatives (prior to each respective class review)
5. Pharmacotherapy class re-reviews……..……..UMass Clinical Pharmacy Services
    - Central Alpha-Agonists – AHFS 240816
    - Direct Vasodilators – AHFS 240820
    - Peripheral Adrenergic Inhibitors – AHFS 240832
    - Hypotensive Agents, Miscellaneous – AHFS 240892
    - Alpha-Adrenergic Blocking Agents – AHFS 242000
    - Beta-Adrenergic Blocking Agents – AHFS 242400
    - Dihydropyridines – AHFS 242808
    - Calcium-Channel Blocking Agents, Miscellaneous – AHFS 242892
    - Angiotensin-Converting Enzyme Inhibitors – AHFS 243204
    - Angiotensin II Receptor Antagonists – AHFS 243208
    - Mineralocorticoid (Aldosterone) Receptor Antagonists – AHFS 243220
    - Renin Inhibitors – AHFS 243240
    - Loop Diuretics – AHFS 402808
    - Potassium-Sparing Diuretics – AHFS 402816
    - Thiazide Diuretics – AHFS 402820
    - Thiazide-Like Diuretics – AHFS 402824
    - Vasopressin Antagonists – AHFS 402828
    - Diuretics, Miscellaneous – AHFS 402892
    - Alzheimer's Agents
        - *Parasympathomimetic (Cholinergic) Agents – AHFS Class 120400* (current brands to be included: Adlarity®, Aricept®, and Exelon® only)
        - *Central Nervous System Agents, Miscellaneous – AHFS Class 289200* (current brands to be included: Aduhelm®, Leqembi®, Namenda®, Namenda XR®, and Namzaric® only)
6. Pharmacotherapy class initial review……..……..UMass Clinical Pharmacy Services
    - Skin and Mucus Membrane Immunomodulators – AHFS 849200 (current brands to be included: Bimzelx®, Adbry®, Dupixent®, Ilumya®, Siliq®, Skyrizi®, Sotyktu®, Spevigo®, Stelara®, Taltz®, Tremfya® only)
7. New business .....Alabama Medicaid
8. Results of voting announced……..…….....…….Chair
9. Next meeting dates
    - August 21, 2024
    - November 6, 2024
10. Adjourn

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Central Alpha-Agonists
AHFS Class 240816
May 8, 2024

I. Overview

Drugs to treat hypertension are among the most frequently prescribed pharmacologic agents. The incidence of hypertension increases with age, and the proper selection of an antihypertensive agent is an important issue.[1,2] While a multitude of neurohormonal, renal, and vascular mechanisms have been proposed as contributors to hypertension, no specific cause can be assigned in most cases.[3] Antihypertensive agents are separated into broad classes depending on which aspect of blood pressure regulation they affect: sodium and water balance, the sympathetic nervous system, resistance from vascular smooth muscle, or the renin-angiotensin-aldosterone system (RAAS).[4] Most patients will require therapy with more than one agent to achieve adequate blood pressure control. When monotherapy fails to achieve the blood pressure goal, then a second agent from a different class should be added to the treatment regimen.[1]

The central alpha-agonists are approved for the treatment of hypertension. They lower blood pressure primarily through stimulation of α_2-adrenergic receptors in the central nervous system (CNS). This action inhibits sympathetic vasomotor centers, causing decreased sympathetic outflow from the CNS and an associated increase in vagal tone. Sympathetic activity is reduced while parasympathetic activity is increased. This leads to a reduction in total peripheral resistance, systolic and diastolic blood pressure, baroreceptor reflexes, heart rate, and cardiac output.[3,5-8] Plasma renin activity is also affected by the central α-agonists, but the relationship between this and their hypotensive effects has not been fully elucidated. Chronic central α-agonist use is associated with sodium and fluid retention, which may require concomitant diuretic therapy.[3] Methyldopa is available in combination with a thiazide diuretic. Thiazide diuretics inhibit the reabsorption of sodium and chloride in the cortical thick ascending limb of the loop of Henle and the early distal tubules. This action leads to an increase in the urinary excretion of sodium and chloride.[5-8]

The central α-agonists that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All of the products are available in a generic formulation. This class was last reviewed in May 2022.

Table 1. Central Alpha-Agonists Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Clonidine	extended-release tablet, tablet, transdermal patch	N/A	clonidine
Guanfacine	tablet	N/A	guanfacine
Methyldopa	tablet	N/A	methyldopa
Methyldopate	injection^	N/A	N/A

*Generic is available in at least one dosage form or strength.
^Product is primarily administered in an institution.
PDL=Preferred Drug List
N/A=Not available

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the central α-agonists are summarized in Table 2.

Table 2. Treatment Guidelines Using the Central Alpha-Agonists

Clinical Guideline	Recommendations
Eighth Joint National Committee (JNC 8): **2014 Evidence-based Guideline for the Management of High Blood Pressure in Adults (2014)[1]**	• Pharmacologic treatment should be initiated in patients ≥60 years of age to lower blood pressure at systolic blood pressure ≥150 mm Hg or diastolic blood pressure ≥90 mm Hg and to a goal systolic blood pressure <150 mm Hg and goal diastolic blood pressure <90 mm Hg. Adjustment of treatment is not necessary if treatment results in lower blood pressure and treatment is well tolerated and without adverse effects on health or quality of life. • In patients <60 years of age, pharmacologic treatment should be initiated to lower blood pressure at diastolic blood pressure ≥90 mm Hg to a goal diastolic blood pressure <90 mm Hg. • In patients <60 years of age, pharmacologic treatment should be initiated to lower blood pressure at systolic blood pressure ≥150 mm Hg to a goal diastolic blood pressure <140 mm Hg. • For patients ≥18 years of age with chronic kidney disease or diabetes, pharmacologic treatment should be initiated to lower blood pressure at systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg and to a goal systolic blood pressure <140 mm Hg and goal diastolic blood pressure <90 mm Hg. • Initial antihypertensive treatment for the general nonblack population, including those with diabetes, should include thiazide-type diuretic, calcium channel blocker (CCB), ACE inhibitor, or ARB. • Initial antihypertensive treatment for the general black population, including those with diabetes, should include thiazide-type diuretic or CCB. • For patients ≥18 years of age with chronic kidney disease regardless of race or diabetes status, initial (or add-on) treatment should include an ACE inhibitor or ARB to improve kidney outcomes. • The main goal of antihypertensive treatment is to attain and maintain goal blood pressure. • If goal blood pressure is not attained within a month of treatment, the dose of the initial drug should be increased or second drug from the thiazide-type diuretic, CCB, ACE inhibitor, or ARB classes should be added. • If goal is not achieved with two drugs, a third drug from the thiazide-type diuretic, CCB, ACE inhibitor, or ARB classes should be added. • An ACE inhibitor and ARB should not be used together. • Antihypertensive classes can be used if the patient is unable to achieve goal blood pressure with three agents or had a contraindication to a preferred class. • If blood pressure is not able to be achieved or in complicated patients, referral to a hypertension specialist may be indicated.
International Society of Hypertension: **Global Hypertension Practice Guidelines (2020)[9]**	<u>Lifestyle modifications</u> • Lifestyle modification is the first line of antihypertensive treatment. • Salt reduction: Reduce salt added when preparing foods, and at the table. Avoid or limit consumption of high salt foods such as soy sauce, fast foods and processed food including breads and cereals high in salt. • Healthy diet: Eating a diet that is rich in whole grains, fruits, vegetables, polyunsaturated fats and dairy products and reducing food high in sugar, saturated fat and trans fats, such as the DASH diet. • Healthy drinks: Moderate consumption of coffee, green and black tea. Other beverages that can be beneficial include karkadé (hibiscus) tea, pomegranate juice, beetroot juice and cocoa. • Moderation of alcohol consumption: The recommended daily limit for alcohol consumptions is 2 standard drinks for men and 1.5 for women (10 g

Clinical Guideline	Recommendations
	alcohol/standard drink). Avoid binge drinking. • Weight reduction: Body weight control is indicated to avoid obesity. Particularly abdominal obesity should be managed. Ethnic-specific cut-offs for BMI and waist circumference should be used. Alternatively, a waist-to-height ratio <0.5 is recommended for all populations. • Smoking cessation: Smoking is a major risk factor for cardiovascular disease (CVD), COPD and cancer. Smoking cessation and referral to smoking cessation programs are advised. • Regular physical activity: Studies suggest that regular aerobic and resistance exercise may be beneficial for both the prevention and treatment of hypertension. Moderate intensity aerobic exercise (walking, jogging, cycling, yoga, or swimming) for 30 minutes on five to seven days per week Strength training also can help reduce blood pressure. Performance of resistance/strength exercises on two to three days per week. • Reduce stress and induce mindfulness: Stress should be reduced and mindfulness or meditation introduced into the daily routine. • Reduce exposure to air pollution and cold temperature: Evidence from studies support a negative effect of air pollution on blood pressure in the long-term. <u>Pharmacological Treatment</u> • Ideal characteristics of drug treatment o Treatments should be evidence-based in relation to morbidity/mortality prevention. o Use a once-daily regimen which provides 24-hour blood pressure control. o Treatment should be affordable and/or cost-effective relative to other agents. o Treatments should be well-tolerated. o Evidence of benefits of use of the medication in populations to which it is to be applied. • General scheme for drug treatment o Lifestyle modification is the first line of antihypertensive treatment. o Grade 1 hypertension (BP 140 to 159/ 90 to 99): Immediate drug treatment in high-risk patients or those with CVD, chronic kidney disease (CKD), diabetes mellitus (DM), or hypertension-mediated organ damage (HMOD). Drug treatment after three to six months of lifestyle intervention if BP still not controlled in low to moderate risk patients. o Grade 2 hypertension (BP ≥160/100): Immediate drug treatment in all patients. • Core drug-treatment strategy o Step 1: Dual low-dose combination (ACE inhibitor or ARB plus dihydropyridine-calcium channel blockers (DHP-CCB)); consider monotherapy in low-risk grade 1 hypertension or in very old (≥80 years) or frail patients; consider ACE/ARB plus thiazide-like diuretic in post-stroke, very elderly, incipient HF, or CCB intolerance; consider ACE/ARB plus DHP-CCB or DHP-CCB plus thiazide-like diuretics in black patients. o Step 2: Dual full-dose combination (ACE inhibitor or ARB plus DHP-CCB); consider monotherapy in low-risk grade 1 hypertension or in very old (≥80 years) or frail patients; consider ACE/ARB plus thiazide-like diuretic in post-stroke, very elderly, incipient HF, or CCB intolerance. o Step 3: Triple combination (ACE/ARB plus DHP-CCB plus thiazide-like diuretic). o Step 4, resistant hypertension: triple combination plus spironolactone or other drug, alternatives include amiloride, doxazosin, eplerenone, clonidine, or β-blocker. Caution with spironolactone or other potassium sparing diuretics when estimated GFR <45 mL/min/1.73m^2 or K+ >4.5

Clinical Guideline	Recommendations
	mmol/L. o Consider β-blockers at any treatment step when there is a specific indication for their use, e.g., heart failure, angina, post-MI, atrial fibrillation, or younger women planning pregnancy or pregnant.
Hypertension Canada: **2020 Guidelines for the Prevention, Diagnosis, Risk Assessment, and Treatment of Hypertension in Adults and Children (2020)[10]**	<u>Indications for drug therapy for adults with hypertension without compelling indications for specific agents</u> • Antihypertensive therapy should be prescribed for average diastolic blood pressure (DBP) measurements of ≥100 mmHg or average systolic blood pressure (SBP) measurements of ≥160 mmHg in patients without macrovascular target organ damage or other cardiovascular risk factors. • Antihypertensive therapy should be strongly considered for average DPB readings ≥90 mmHg or for average SBP readings ≥140 mmHg in the presence of macrovascular target organ damage or other independent cardiovascular risk factors. • For high-risk patients, aged 50 years or older, with SBP levels ≥130 mmHg, intensive management to target a SBP <120 mmHg should be considered. Patient selection for intensive management is recommended and caution should be taken in certain high-risk groups. <u>Indications for drug therapy for adults with diastolic and with or without systolic hypertension</u> • Initial therapy should be with either monotherapy or single pill combination (SPC). o Recommended monotherapy choices are: ▪ A thiazide/thiazide-like diuretic, with longer-acting diuretics preferred; ▪ A β-blocker (in patients <60 years of age); ▪ An angiotensin-converting enzyme (ACE) inhibitor (in nonblack patients); ▪ An angiotensin receptor blocker (ARB); or ▪ A long-acting calcium channel blocker (CCB). o Recommended SPC choices are those in which an ACE inhibitor is combined with a CCB, ARB with a CCB, or ACE inhibitor or ARB with a diuretic. o Hypokalemia should be avoided in patients treated with thiazide/thiazide-like diuretic monotherapy. • Additional antihypertensive drugs should be used if target BP levels are not achieved with standard-dose monotherapy. Add-on drugs should be chosen from first-line choices. Useful choices include a thiazide/thiazide-like diuretic or CCB with either: ACE inhibitor, ARB, or β-blocker. Caution should be exercised in combining a nondihydropyridine CCB and a β-blocker. The combination of an ACE inhibitor and an ARB is not recommended. • If BP is still not controlled with a combination of two or more first-line agents, or there are adverse effects, other antihypertensive drugs may be added. • Possible reasons for poor response to therapy should be considered. • α-Blockers are not recommended as first-line agents for uncomplicated hypertension; β-blockers are not recommended as first-line therapy for uncomplicated hypertension in patients ≥60 years of age; and ACE inhibitors are not recommended as first-line therapy for uncomplicated hypertension in black patients. However, these agents may be used in patients with certain comorbid conditions or in combination therapy. <u>Indications for drug therapy for adults with isolated systolic hypertension</u> • Initial therapy should be single-agent therapy with a thiazide/thiazide-like diuretic, a long-acting dihydropyridine CCB, or an ARB. If there are adverse effects, another drug from this group should be substituted. Hypokalemia should

Clinical Guideline	Recommendations
	be avoided in patients treated with thiazide/thiazide-like diuretic monotherapy. • Additional antihypertensive drugs should be used if target BP levels are not achieved with standard-dose monotherapy. Add-on drugs should be chosen from first-line options. • If BP is still not controlled with a combination of two or more first-line agents, or there are adverse effects, other classes of drugs (such as α-blockers, ACE inhibitors, centrally acting agents, or nondihydropyridine CCBs) may be combined or substituted. • Possible reasons for poor response to therapy should be considered. • α-Blockers are not recommended as first-line agents for uncomplicated isolated systolic hypertension; and β-blockers are not recommended as first-line therapy for isolated systolic hypertension in patients ≥60 years of age. However, both agents may be used in patients with certain comorbid conditions or in combination therapy. <u>Guidelines for hypertensive patients with coronary artery disease (CAD)</u> • For most hypertensive patients with CAD, an ACE inhibitor or ARB is recommended. • For hypertensive patients with CAD, but without coexisting systolic heart failure, the combination of an ACE inhibitor and ARB is not recommended. • For high-risk hypertensive patients, when combination therapy is being used, choices should be individualized. The combination of an ACE inhibitor and a dihydropyridine CCB is preferable to an ACE inhibitor and a thiazide/thiazide-like diuretic in selected patients. • For patients with stable angina pectoris but without previous heart failure, myocardial infarction, or coronary artery bypass surgery, either a β-blocker or CCB can be used as initial therapy. • Short-acting nifedipine should not be used. • When decreasing SBP to target levels in patients with established CAD (especially if isolated systolic hypertension is present), be cautious when the DBP is ≤60 mmHg because of concerns that myocardial ischemia might be exacerbated, especially in patients with left ventricular hypertrophy (LVH). <u>Guidelines for patients with hypertension who have had a recent myocardial infarction</u> • Initial therapy should include a β-blocker as well as an ACE inhibitor. • An ARB can be used if the patient is intolerant of an ACE inhibitor. • CCBs may be used in patients after myocardial infarction when β-blockers are contraindicated or not effective. Nondihydropyridine CCBs should not be used when there is heart failure, evidenced by pulmonary congestion on examination or radiography. <u>Treatment of hypertension in association with heart failure</u> • In patients with systolic dysfunction (ejection fraction <40%), ACE inhibitors and β-blockers are recommended for initial therapy. Aldosterone antagonists (mineralocorticoid receptor antagonists) may be combined in treatment for patients with a recent cardiovascular hospitalization, acute myocardial infarction, elevated B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide level, or New York Heart Association (NYHA) Class II-IV symptoms. Careful monitoring for hyperkalemia is recommended when combining an aldosterone antagonist with ACE inhibitor or ARB treatment. Other diuretics are recommended as additional therapy if needed. Beyond considerations of BP control, doses of ACE inhibitors or ARBs should be titrated to those reported to be effective in trials unless adverse effects become manifest. • An ARB is recommended if ACE inhibitors are not tolerated.

Clinical Guideline	Recommendations

	• A combination of hydralazine and isosorbide dinitrate is recommended if ACE inhibitors and ARBs are contraindicated or not tolerated.
	• For hypertensive patients whose BP is not controlled, an ARB may be combined with an ACE inhibitor and other antihypertensive drug treatment. Careful monitoring should be used if combining an ACE inhibitor and an ARB because of potential adverse effects such as hypotension, hyperkalemia, and worsening renal function. Additional therapies may also include dihydropyridine CCBs.
	• An angiotensin receptor-neprilysin inhibitor (ARNI) should be used in place of an ACE inhibitor or ARB for patients with HFrEF (<40%) who remain symptomatic despite treatment with appropriate dose of guideline directed HF therapy. Eligible patients must have a serum potassium <5.2 mmol/L, an eGFR ≤30 mL/min/1.73m^2 and close surveillance of serum potassium and creatinine.
	
	<u>Treatment of hypertension in association with stroke</u>
	• BP management in acute ischemic stroke (onset to 72 hours)
	  o Please refer to Stroke Best Practice recommendations.
	• BP management after acute ischemic stroke
	  o Strong consideration should be given to the initiation of antihypertensive therapy after the acute phase of a stroke or transient ischemic attack.
	  o After the acute phase of a stroke, BP-lowering treatment is recommended to a target of consistently <140/90 mmHg.
	  o Treatment with an ACE inhibitor and thiazide/thiazide-like diuretic combination is preferred.
	  o For patients with stroke, the combination of an ACE inhibitor and ARB is not recommended.
	• BP management in hemorrhagic stroke (onset to 72 hours)
	  o Please refer to Stroke Best Practice recommendations.
	
	<u>Treatment of hypertension in association with LVH</u>
	• Hypertensive patients with LVH should be treated with antihypertensive therapy to decrease the rate of subsequent cardiovascular events.
	• The choice of initial therapy can be influenced by the presence of LVH. Initial therapy can be drug treatment using ACE inhibitors, ARBs, long-acting CCBs, or thiazide/thiazide-like diuretics. Direct arterial vasodilators such as hydralazine or minoxidil should not be used.
	
	<u>Treatment of hypertension in association with nondiabetic chronic kidney disease</u>
	• Individualize BP targets in patients with chronic kidney disease. Consider intensive targets (SBP <120 mmHg) in appropriate patients.
	• For patients with hypertension and proteinuric chronic kidney disease (urinary protein >150 mg per 24 hours or albumin to creatinine ratio >30 mg/mmol), initial therapy should be an ACE inhibitor or an ARB if there is intolerance to ACE inhibitors.
	• In most cases, combination therapy with other antihypertensive agents might be needed to reach target BP levels.
	• The combination of an ACE inhibitor and ARB is not recommended for patients with nonproteinuric chronic kidney disease.
	
	<u>Treatment of hypertension in association with renovascular disease</u>
	• Patients with hypertension attributable to atherosclerotic renal artery stenosis should be primarily medically managed because renal angioplasty and stenting offers no benefit over optimal medical therapy alone.
	• Renal artery angioplasty and stenting for atherosclerotic hemodynamically significant renal artery stenosis could be considered for patients with uncontrolled hypertension resistant to maximally tolerated pharmacotherapy, progressive renal

Clinical Guideline	Recommendations
	function loss, and acute pulmonary edema. • Patients with confirmed renal fibromuscular dysplasia (FMD) should be referred to a hypertension specialist. • Renal artery angioplasty without stenting is recommended for treatment of FMD-related renal artery stenosis. Stenting is not recommended unless needed because of a periprocedural dissection. Surgical revascularization should be considered in cases of complex lesions less amendable to angioplasty, stenosis associated with complex aneurysm, and restenosis despite two unsuccessful attempts of angioplasty. <u>Treatment of hypertension in association with diabetes mellitus</u> • Persons with diabetes mellitus should be treated to attain SBP of <130 mmHg and DBP of <80 mmHg. • For persons with cardiovascular or kidney disease, including microalbuminuria, or with cardiovascular risk factors in addition to diabetes and hypertension, an ACE inhibitor or an ARB is recommended as initial therapy. • For persons with diabetes and hypertension not included in other guidelines in this section, appropriate choices include (in alphabetical order): ACE inhibitors, ARBs, dihydropyridine CCBs, and thiazide/thiazide-like diuretics. • If target BP levels are not achieved with standard-dose monotherapy, additional antihypertensive therapy should be used. For persons in whom combination therapy with an ACE inhibitor is being considered, a dihydropyridine CCB is preferable to a thiazide/thiazide-like diuretic. <u>Resistant hypertension</u> • Resistant hypertension is defined as BP above target despite three or more BP-lowering drugs at optimal doses preferably including a diuretic (and usually a renin-angiotensin-aldosterone system blocker and a CCB. • Accurate office and out-of-office BP measurement is essential. • Other reasons for apparent resistant hypertension should be eliminated before diagnosing true resistant hypertension, including nonadherence, white coat effect, and secondary hypertension. • Pharmacotherapy with the additional use of spironolactone, bisoprolol, doxazosin, amiloride, eplerenone, or clonidine with the baseline regimen decreases BP significantly, with the greatest BP-lowering shown with spironolactone. • Patients with resistant hypertension should be referred to providers with expertise in diagnosis and management of hypertension. <u>Hypertension and pediatrics</u> • BP should be measured regularly in children three years of age or older; the auscultatory method is the gold-standard at present. • Initial therapy should be monotherapy, with an ACE inhibitor or ARB (not first-line in black children), or a long-acting dihydropyridine CCB. • The treatment t goal is systolic and diastolic office BP and/or ABPM < 95th percentile or <90th percentile in children with risk factors or target organ damage. • Complex cases should be referred to an expert in pediatric hypertension. <u>Hypertension and pregnancy</u> • Up to 7% of pregnancies are complicated by a hypertensive disorder of pregnancy, and approximately 5% of women will have chronic hypertension when they become pregnant. • The prevalence of hypertension in pregnancy is expected to increase with women becoming pregnant later in their reproductive years and the increasing prevalence of cardiovascular comorbidities such as increased preconception body mass index

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	and maternal diabetes. • The possibility of pregnancy should be considered when managing women with hypertension who are of reproductive age. • Preconception counselling should be offered to all women with hypertension who are considering pregnancy. • ACE inhibitor and ARB therapy should be avoided before conception and during pregnancy unless there is a compelling indication for their use (i.e., proteinuric kidney disease). • Hypertension during pregnancy can increase the risk of adverse maternal and fetal outcomes, including an increased risk of preeclampsia, placental abruption, prematurity, small for gestational age infants, stillbirth, and maternal renal and retinal injury, thus generally requires involvement of an interdisciplinary team including obstetrical care providers. • Antihypertensive therapy is recommended for average SBP measurements of ≥140 mmHg or DBP measurements of ≥90 mmHg in pregnant women with chronic hypertension, gestational hypertension, or preeclampsia. Initial antihypertensive therapy should be monotherapy from the following first-line drugs: oral labetalol, oral methyldopa, long-acting oral nifedipine, or other oral b-blockers (acebutolol, metoprolol, pindolol, and propranolol). Other antihypertensive drugs can be considered as second-line drugs including: clonidine, hydralazine, and thiazide diuretics. • Women with severe hypertension with SBP ≥160 mmHg or DBP ≥110 mmHg in pregnancy or postpartum require urgent antihypertensive therapy because it is considered an obstetrical emergency. • Antihypertensive drugs used in breastfeeding women include: labetalol, methyldopa, long-acting nifedipine, enalapril, or captopril.
European Society of Hypertension: **2023 Guidelines for the management of arterial hypertension (2023)[11]**	General recommendations for antihypertensive drug treatment • BP lowering should be prioritized over the selection of specific antihypertensive drug classes because treatment benefit largely originates from BP reduction. • Five major drug classes including, ACE inhibitors, ARBs, β-blockers, CCBs, and Thiazide/Thiazide-like diuretics have effectively reduced blood pressure and cardiovascular events in randomized controlled trials. These drugs and their combinations are recommended as the basis of antihypertensive treatment strategies. • Initiation of therapy with a two-drug combination is recommended for most hypertensive patients. Preferred combinations should comprise a RAS blocker (either an ACE inhibitor or an ARB) with a CCB or thiazide/thiazide-like diuretic. Other combinations of the five major drug classes can be used. • Initiation with monotherapy can be considered in patients with: grade 1 hypertension and low-risk if BP is only marginally elevated (less than 150 mmHg SBP and 95 mmHg DBP) high-normal BP and very high cardiovascular risk, frailty and/or and advance age. • If BP is not controlled with the initial two-drug combination by using the maximum recommended and tolerated dose of the respective components, treatment should be increased to a three-drug combination, usually a RAS blocker plus CCB plus thiazide/thiazide-like diuretic. • If BP is not controlled with a three-drug combination by using the maximum recommended and tolerated dose of the respective components, it is recommended to extend treatment according to the recommendations for resistant hypertension. • The use of single pill combinations should be preferred at any treatment step (i.e. during initiation of therapy with a two-drug combination and at any other step of treatment). • β-blocker should be used at initiation of therapy or at any treatment step as guideline-directed medical therapy (e.g., heart failure with reduced ejection

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	fraction, anti-ischemic therapy in chronic coronary syndromes, heart rate control in atrial fibrillation). • β-blockers can be considered in the presence of several other conditions in which their use can be favorable. • The combination of two RAS blockers is not recommended due to increased risk of adverse events, in particular AKI. True-resistant hypertension • In resistant hypertension, it is recommended to reinforce lifestyle measures. • Drugs that can be considered as additional therapy in patients with resistant hypertension are preferably spironolactone (or other MRA), or β-blocker or Alpha-1 blockers or centrally acting agents (clonidine), or amiloride. • Thiazide/thiazide-like diuretics are recommended in resistant hypertension if estimated eGFR is ≥30 mL/min/1.73m^2. • Loop diuretics may be considered in patients with an estimated eGFR < 45 mL/min/1.73m^2 and should be used if eGFR falls below 30 mL/min/1.73m^2. • Chlorthalidone (12.5 to 25 mg once daily) could be used with or without a loop diuretic if eGFR is <30 mL/min/1.73m^2. • Renal deprivation can be considered as an additional treatment option in patients with resistant hypertension if eGFR is >40 mL/min/1.73m^2. • Patients with resistant hypertension should be followed very closely. Follow-up includes periodical ambulatory blood pressure monitoring and assessment of hypertension-mediated organ damage, particularly kidney function and serum potassium levels. Regular use of home blood pressure monitoring and monitoring of drug adherence are desirable.
National Institute for Health and Clinical Excellence: **Hypertension in adults: diagnosis and management (2019)**[12]	Choosing antihypertensive drug treatment (for people with or without type II diabetes) • Where possible, recommend treatment with drugs taken only once a day. • Prescribe non-proprietary drugs where these are appropriate and minimize cost. • Offer people with isolated systolic hypertension (systolic blood pressure ≥160 mmHg) the same treatment as people with both raised systolic and diastolic blood pressure. • Offer antihypertensive drug treatment to women of child-bearing potential with diagnosed hypertension in line with recommendations in this guideline. For women considering pregnancy or who are pregnant or breastfeeding, manage hypertension in line with the recommendations on Management of pregnancy with chronic hypertension and Breastfeeding in 'Hypertension in pregnancy'. • When choosing antihypertensive drug treatment for adults of black African or African-Caribbean family origin, consider an angiotensin II receptor blocker, in preference to an angiotensin-converting enzyme inhibitor. Step one treatment • Patients <55 years of age should be offered a step one antihypertensive with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). • Offer an ACE inhibitor or an ARB to adults starting step 1 antihypertensive treatment who have type II diabetes and are of any age or family origin or those aged <55 years but not of black African or African-Caribbean family origin. • If an ACE inhibitor is not tolerated, offer an ARB. • Do not combine an ACE inhibitor with an ARB for the treatment of hypertension. • Offer a calcium channel blocker (CCB) to adults starting step 1 antihypertensive treatment who are >55 years of age and do not have diabetes and are of black African or African-Caribbean family origin and do not have type II diabetes and

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	of any age. • If a CCB is not suitable, for example because of edema or intolerance, or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic. • If diuretic treatment is to be initiated or changed, offer a thiazide-like diuretic, such as indapamide in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide. • For adults with hypertension who are already receiving treatment with bendroflumethiazide or hydrochlorothiazide, who have stable, well-controlled blood pressure, continue with their treatment. <u>Step two treatment</u> • Before considering next step treatment for hypertension discuss with the person if they are taking their medicine as prescribed and support adherence in line with NICE's guideline on "Medicines adherence: involving patients decisions about prescribed medicines and supporting adherence". • If hypertension is not controlled with a step one treatment of an ACE inhibitor or ARB, offer choice of one of the following drugs in addition to the step one treatment: a CCB or a thiazide-like diuretic. • If hypertension is not controlled in adults taking step one treatment of a CCB, offer the choice of one of the following drugs in addition to the step one treatment: an ACE inhibitor or an ARB or a thiazide-like diuretic. • If hypertension is not controlled in adults of black African or African–Caribbean family origin who do not have type 2 diabetes taking step one treatment, consider an ARB, in preference to an ACE inhibitor, in addition to step one treatment. <u>Step three treatment</u> • Before considering step three treatment, review the person's medications to ensure they are being taken at the optimal doses and discuss adherence (see recommendation under step two). • If hypertension is not controlled in adults taking step two treatment, offer a combination of an ACE inhibitor or ARB and a CCB and a thiazide-like diuretic. <u>Step four treatment</u> • If hypertension is not controlled in adults taking the optimal tolerated doses of an ACE inhibitor or an ARB plus a CCB and a thiazide-like diuretic, regard them as having resistant hypertension. • Before considering further treatment for a person with resistant hypertension, confirm elevated clinic blood pressure measurements using ambulatory or home blood pressure recordings, assess for postural hypotension, and discuss adherence. • For people with confirmed resistant hypertension, consider adding a fourth antihypertensive drug as step four treatment or seeking specialist advice. • Consider further diuretic therapy with low-dose spironolactone for adults with resistant hypertension starting step four treatment who have a blood potassium level of 4.5 mmol/l or less. Use particular caution in people with a reduced estimated glomerular filtration rate because they have an increased risk of hyperkalemia. • When using further diuretic therapy for step four treatment of resistant hypertension, monitor blood sodium and potassium and renal function within one month of starting treatment and repeat as needed thereafter. • Consider an alpha-blocker or beta-blocker for adults with resistant hypertension starting step four treatment who have a blood potassium level of more than 4.5 mmol/l. • If blood pressure remains uncontrolled in people with resistant hypertension

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	taking the optimal tolerated doses of four drugs, seek specialist advice.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in Blacks (2010)**[13]	• To attain and maintain blood pressure (BP) below target levels, multiple antihypertensive drugs will be required in most hypertensive blacks. • Use of two-drug combination therapy when SBP is >15 mm Hg and/or DBP is >10 mm Hg above goal levels is increasingly recommended as first-line therapy. • Two-drug regimens have generally contained a thiazide-type diuretic; however, the combination of a calcium channel blocker (CCB) with either an ACE inhibitor or an ARB has been shown equally efficacious in BP lowering but with demonstrated superiority (CCB+ACE) for hard clinical outcomes compared with the same ACE inhibitor plus a thiazide-type diuretic. • In secondary prevention patients, the combination therapy should include a drug(s) with the appropriate compelling indications. • Certain classes of antihypertensive medications, specifically diuretics and CCBs, lower BP on average more than β-blockers and renin-angiotensin system (RAS) blockers in black patients when used as monotherapies. • In the absence of compelling indications, when BP is near goal levels, monotherapy with a diuretic or a CCB is preferred. • Lifestyle modifications should be initiated in all patients with hypertension, whether or not pharmacotherapy is planned. • ACE inhibitors or ARBs are recommended as alternative monotherapy options in the treatment of hypertension in blacks. The rationale for their lower tier monotherapy recommendation is because they have consistently achieved lesser average reductions in BP relative to that observed with monotherapy using either a diuretic or CCB.
Kidney Disease Improving Clinical Outcomes Group: **KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease (2021)**[14]	<u>Blood pressure measurement</u> • The Work Group recommends standardized office blood pressure (BP) measurement in preference to routine office BP measurements for the management of high BP in adults. • The Work Group suggests that out-of-office BP measurements with ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM) be used to complement standardized office BP readings for the management of high BP. <u>Lifestyle interventions for lowering BP in patients with chronic kidney disease (CKD) not receiving dialysis</u> • The Work Group suggests targeting a sodium intake <2 grams of sodium per day (or <90 mmol of sodium per day, or <5 grams of sodium chloride per day) in patients with high BP and CKD. • The Work Group suggests that patients with high BP and CKD be advised to undertake moderate-intensity physical activity for a cumulative duration of at least 150 minutes per week, or to a level compatible with their cardiovascular and physical tolerance. <u>BP management in patients with CKD, with or without diabetes, not receiving dialysis</u> • The Work Group suggests that adults with high BP and CKD be treated with a target systolic BP (SBP) of <120 mmHg, when tolerated, using standardized office BP measurement. • The Work Group recommends starting renin-angiotensin-system inhibitors (RASi) (angiotensin-converting enzyme inhibitor [ACEi] or angiotensin II receptor blocker [ARB]) for people with high BP, CKD, and severely increased albuminuria without diabetes. • The Work Group suggests starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately increased albuminuria without diabetes. • The Work Group recommends starting RASi (ACEi or ARB) for people with

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	high BP, CKD, and moderately-to-severely increased albuminuria with diabetes. • The Work Group recommends avoiding any combination of ACEi, ARB, and direct renin inhibitor (DRI) therapy in patients with CKD, with or without diabetes. BP management in kidney transplant recipients • Treat adult kidney transplant recipients with high BP to a target BP of <130 mmHg systolic and <80 mmHg diastolic using standardized office BP measurement. • The Work Group recommends that a dihydropyridine calcium channel blocker (CCB) or an ARB be used as the first-line antihypertensive agent in adult kidney transplant recipients. BP management in children with CKD • The Work Group suggests that in children with CKD, 24-hour mean arterial pressure by ABPM should be lowered to <50th percentile for age, sex, and height.
American Diabetes Association: **Standards of Medical Care in Diabetes (2023)**[15]	Hypertension/blood pressure control • Blood pressure should be measured at every routine visit. When possible, patients found to have elevated blood pressure (systolic blood pressure 120 to 129 mmHg and diastolic <80 mmHg) should have blood pressure confirmed using multiple readings, including measurements on a separate day, to diagnose hypertension. Patients with blood pressure ≥180/110 and cardiovascular disease could be diagnosed with hypertension at a single visit. • All hypertensive patients with diabetes should monitor their blood pressure at home. • For patients with diabetes and hypertension, blood pressure targets should be individualized through a shared decision-making process that addresses cardiovascular risk, potential adverse effects of antihypertensive medications, and patient preferences. • Individuals with diabetes and hypertension qualify for antihypertensive drug therapy when the blood pressure is persistently elevated ≥130/80 mmHg. The on-treatment target blood pressure goal is <130/80 mmHg, if it can be safely attained. • In pregnant patients with diabetes and preexisting hypertension, a blood pressure target of 110 to 135/85 is suggested in the interest of reducing the risk for accelerated maternal hypertension and minimizing impaired fetal growth. • For patients with blood pressure >120/80, lifestyle intervention consists of weight loss when indicated, a Dietary Approaches to Stop Hypertension (DASH)-style eating pattern including reducing sodium and increasing potassium intake, moderation of alcohol intake, and increased physical activity. • Patients with confirmed office-based blood pressure ≥130/80 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of pharmacologic therapy to achieve blood pressure goals. • Patients with confirmed office-based blood pressure ≥160/100 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of two drugs or a single pill combination of drugs demonstrated to reduce cardiovascular events in patients with diabetes. • Treatment for hypertension should include drug classes demonstrated to reduce cardiovascular events in patients with diabetes (ACE inhibitors, angiotensin receptor blockers, thiazide-like diuretics, or dihydropyridine calcium channel blockers). ACE inhibitors or angiotensin receptor blockers are recommended first-line therapy for hypertension in people with diabetes and coronary artery disease. • Multiple-drug therapy is generally required to achieve blood pressure targets (but not a combination of ACE inhibitors and angiotensin receptor blockers).

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	• An ACE inhibitor or angiotensin receptor blocker, at the maximum tolerated dose indicated for blood pressure treatment, is the recommended first-line treatment for hypertension in patients with diabetes and urinary albumin–to–creatinine ratio ≥300 mg/g creatinine or 30 to 299 mg/g creatinine. If one class is not tolerated, the other should be substituted. • For patients treated with an ACE inhibitor, angiotensin receptor blocker, or diuretic, serum creatinine/estimated glomerular filtration rate and serum potassium levels should be monitored at least annually. • Patients with hypertension who are not meeting blood pressure targets on three classes of antihypertensive medications (including a diuretic) should be considered for mineralocorticoid receptor antagonist therapy. Chronic kidney disease • At least once a year, assess urinary albumin (e.g., spot urinary albumin–to–creatinine ratio) and estimated glomerular filtration rate in patients with type 1 diabetes with duration of five or more years and in all patients with type 2 diabetes. • In people with established diabetic kidney disease, urinary albumin (e.g., spot urinary albumin-to-creatinine ratio) and estimated glomerular filtration rate should be monitored one to four times per year depending on the stage of the disease. Optimize glucose control to reduce the risk or slow the progression of chronic kidney disease (CKD). • For patients with type 2 diabetes and diabetic kidney disease, use of a sodium-glucose cotransporter 2 inhibitor in patients with an estimated glomerular filtration rate ≥20 mL/min/1.73 m^2 and urinary albumin ≥200 mg/g creatinine is recommended to reduce CKD progression and cardiovascular events. • For patients with type 2 diabetes and diabetic kidney disease, use of a sodium–glucose cotransporter 2 inhibitor is recommended to reduce chronic kidney disease progression and cardiovascular events in patients with an estimated glomerular filtration rate ≥20 mL/min/1.73 m^2 and urinary albumin ranging from normal to 200 mg/g creatinine. • In people with type 2 diabetes and diabetic kidney disease, consider use of sodium–glucose cotransporter 2 inhibitors (if estimated glomerular filtration rate is ≥20 mL/min/1.73 m^2), a glucagon-like peptide 1 agonist, or a nonsteroidal mineralocorticoid receptor antagonist (if estimated glomerular filtration rate is ≥25 mL/min/1.73 m^2) additionally for cardiovascular risk reduction. • In people with chronic kidney disease and albuminuria who are at increased risk for cardiovascular events or chronic kidney disease progression, a nonsteroidal mineralocorticoid receptor antagonist shown to be effective in clinical trials is recommended to reduce chronic kidney disease progression and cardiovascular events. • Optimize blood pressure control and reduce blood pressure variability to reduce the risk or slow the progression of CKD. • Do not discontinue renin-angiotensin system blockade for minor increases in serum creatinine (≤30%) in the absence of volume depletion. • For people with nondialysis-dependent stage 3 or higher CKD, dietary protein intake should be a maximum of 0.8 g/kg body weight per day (the recommended daily allowance). For patients on dialysis, higher levels of dietary protein intake should be considered, since protein energy wasting is a major problem in some dialysis patients. • In nonpregnant patients with diabetes and hypertension, either an ACE inhibitor or an angiotensin receptor blocker is recommended for those with modestly elevated urinary albumin–to–creatinine ratio (30 to 299 mg/g creatinine) and is strongly recommended for those with urinary albumin–to–creatinine ratio ≥300 mg/g creatinine and/or estimated glomerular filtration rate <60 mL/min/1.73 m^2.

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	• Periodically monitor serum creatinine and potassium levels for the development of increased creatinine and hyperkalemia when ACE inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists are used, or hypokalemia when diuretics are used. • An ACE inhibitor or an angiotensin receptor blocker is not recommended for the primary prevention of CKD in patients with diabetes who have normal blood pressure, normal urinary albumin–to–creatinine ratio (<30 mg/g creatinine), and normal estimated glomerular filtration rate. • Patients should be referred for evaluation by a nephrologist if they have continuously increasing urinary albumin levels and/or continuously decreasing estimated glomerular filtration rate and an estimated glomerular filtration rate <30 mL/min/1.73 m^2. • Promptly refer to a nephrologist for uncertainty about the etiology of kidney disease, difficult management issues, and rapidly progressing kidney disease.
American College of Cardiology/American Heart Association Task Force: **Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults (2017)[16]**	<u>Initiation of Blood Pressure (BP) Treatment for Overall Cardiovascular Disease (CVD) Risk</u> • Use of BP-lowering medications is recommended for secondary prevention of recurrent CVD events in patients with clinical CVD and an average systolic blood pressure (SBP) ≥130 mmHg or an average diastolic blood pressure (DBP) of ≥80 mmHg and for primary prevention in adults with an estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk of ≥10% and an average SBP of ≥130 mmHg or an average ≥80 mmHg. • Use of BP-lowering medication is recommended for primary prevention of CVD in adults with no history of CVD and with an estimated 10-year ASCVD risk <10% and an SBP of ≥140 mmHg or a DBP of ≥90 mmHg. • Simultaneous use of an angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), and/or renin inhibitor is potentially harmful and is not recommended to treat adults with hypertension. • For adults with confirmed hypertension and known CVD or 10-year ASCVD risk of ≥10%, a BP target <130/80 mmHg is recommended. For adults with confirmed hypertension without additional markers of increased CVD risk, a BP target <130/80 mmHg may be reasonable. • For initiation of antihypertensive drug therapy, first-line agents include thiazide diuretics, calcium channel blockers (CCBs), and ACE inhibitors or ARBs. • Initiation of antihypertensive drug therapy with two first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended in adults with stage 2 hypertension and an average BP >20/10 mmHg above their BP target. • Initiation of antihypertensive drug therapy with a single antihypertensive drug is reasonable in adults with stage 1 hypertension and BP goal <130/80 mmHg with dosage titration and sequential addition of other agents to achieve the BP target. <u>Stable Ischemic Heart Disease (SIHD)</u> • In adults with SIHD and hypertension, a BP target <130/80 is recommended. • Adults with SIHD and hypertension (BP ≥130/80 mmHg) should be treated with medications [e.g., guideline-directed medical therapy (GDMT) beta-blockers, ACE inhibitors, or ARBs] for compelling indications [e.g., previous myocardial infarction (MI), stable angina] as first-line therapy, with the addition of other drugs (e.g., dihydropyridine CCBs, thiazide diuretics, and/or mineralocorticoid receptor antagonists) as needed to further control hypertension. • In adults with SIHD with angina and persistent uncontrolled hypertension, the addition of dihydropyridine CCBs to GDMT beta-blockers is recommended. • In adults who have had a MI or acute coronary syndrome, it is reasonable to continue GDMT beta-blockers beyond three years as long-term therapy for

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	hypertension. • Beta-blockers and/or CCBs might be considered to control hypertension in patients with coronary artery disease (CAD) had an MI more than three years ago and have angina. <u>Heart Failure</u> • In adults with increased risk of HF, the optimal BP in those with hypertension should be <130 mmHg. • Adults with HFrEF and hypertension should be prescribed GDMT titrated to attain a BP <130/80 mmHg. • Non-dihydropyridine CCBs are not recommended in the treatment of hypertension in adults with HFrEF. • In adults with HFpEF who present with symptoms of volume overload, diuretics should be prescribed to control hypertension. • Adults with HFpEF and persistent hypertension after management of volume overload should be prescribed ACE inhibitors or ARBs and beta-blockers titrated to attain SBP <130 mmHg. <u>CKD</u> • Adults with hypertension and CKD should be treated to a BP goal <130/80 mmHg. • In adults with hypertension and CKD [stage 3 or higher or stage 1 or 2 with albuminuria (≥300 mg/d, or ≥300 mg/g albumin-to-creatinine ratio or the equivalent in the first morning void)], treatment with an ACE inhibitor is reasonable to slow kidney disease progression. Treatment with an ARB may be reasonable if an ACE inhibitor is not tolerated. • After kidney transplantation, it is reasonable to treat patients with hypertension to a BP goal <130/80 mmHg and with a CCB on the basis of improved glomerular filtration rate (GFR) and kidney survival. <u>Cerebrovascular Disease</u> • In adults with intracerebral hemorrhage (ICH) who present with SBP >220 mmHg, it is reasonable to use continuous intravenous (IV) drug infusion and close BP monitoring to lower levels. Immediate lowering of SBP to <140 mmHg in adults with spontaneous ICH who present within six hours of the acute event and have an SBP between 150 mmHg and 220 mmHg is not of benefit to reduce death or severe disability and can be potentially harmful. • Adults with acute ischemic stroke and elevated BP who are eligible for treatment with IV tissue plasminogen activator (tPA) should have their BP slowly lowered to <185/110 mmHg before thrombolytic therapy is initiated. • In adults with an acute ischemic stroke, BP should be <185/110 mmHg before administration of IV tPA and should be maintained below 180/105 mmHg for at least the first 24 hours after initiation drug therapy. • Starting or restarting antihypertensive therapy during hospitalization in patients with BP >140/90 mmHg who are neurologically stable is safe and reasonable to improve long-term BP control, unless contraindicated. • In patient with BP ≥220/120 mmHg who did not receive IV alteplase or endovascular treatment and have no comorbid conditions requiring acute antihypertensive treatment, the benefit of initiating or reinitiating treatment of hypertension within the first 48 to 72 hours is uncertain. It might be reasonable to lower BP by 15% during the first 24 hours after onset of stroke. In patients with BP <220/120 mmHg with the same conditions, initiating or reinitiating treatment of hypertension within the first 48 to 72 hours after an acute ischemic stroke is not effective to prevent death or dependency. • Adults with previously treated stroke or transient ischemic attack should be

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	restarted on antihypertensive treatment after the first few days of the index event to reduce the risk of recurrent stroke and other vascular events. Treatment with a thiazide diuretic, ACE inhibitor, or ARB, or combination treatment consisting of a thiazide diuretic plus ACE inhibitor, is useful. • Adults not previously treated for hypertension who experienced a stroke or transient ischemic attack and have an established BP ≥140/90 mmHg should be prescribed antihypertensive treatment a few days after the index event to reduce the risk of recurrent stroke and other vascular event. • For adults who experience a stroke or transient ischemic attack, selection of specific drugs should be individualized on the basis of patient comorbidities and agent pharmacological class. • For adults who experience a stroke or transient ischemic attack, a BP goal <130/80 mmHg may be reasonable. • For adults with a lacunar stroke, a target SBP goal <130 mmHg may be reasonable. • In adults previously untreated for hypertension who experience an ischemic stroke or transient ischemic attack and have an SBP <140 mmHg and a DBP <90 mmHg, the usefulness of initiating antihypertensive treatment is not well established. <u>Peripheral Artery Disease (PAD)</u> • Adults with hypertension and PAD should be treated similarly to patients with hypertension without PAD. <u>Diabetes Mellitus (DM)</u> • In adults with DM and hypertension, antihypertensive drug treatment should be initiated at a BP of ≥130/80 mmHg with a treatment goal <130/80 mmHg. • In adults with DM and hypertension, all first-line classes of antihypertensive agents (i.e., diuretics, ACE inhibitors, ARBs, and CCBs) are useful and effective. • In adults with DM and hypertension, ACE inhibitors or ARBs may be considered in the presence of albuminuria. <u>Atrial Fibrillation, Valvular Heart Disease, and Aortic disease</u> • Treatment of hypertension can be useful for prevention of recurrence of AF. • In adults with asymptomatic aortic stenosis, hypertension should be treated with pharmacotherapy, starting at a low dose and gradually titrating upward as needed. • In patients with chronic aortic insufficiency, treatment of systolic hypertension with agents that do not slow the heart rate (i.e., avoid beta-blockers) is reasonable. • Beta-blockers are recommended as the preferred antihypertensive agents in patients with hypertension and thoracic aortic disease. <u>Racial and Ethnic Differences in Treatment</u> • In black adults with hypertension but without HF or CKD, including those with DM, initial antihypertensive treatment should include a thiazide-type diuretic or CCB. Two or more antihypertensive medications are recommended to achieve a BP target <130/80 mmHg in most adults with hypertension, especially in black adults with hypertension. <u>Pregnancy</u> • Women with hypertension who become pregnant, or are planning to become pregnant, should be transitioned to methyldopa, nifedipine, and/or labetalol during pregnancy. • Women with hypertension who become pregnant should not be treated with ACE inhibitors, ARBs, or direct renin inhibitors.

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	Older Persons • Treatment of hypertension with an SBP treatment goal <130 mmHg is recommended for noninstitutionalized ambulatory community-dwelling adults (≥65 years of age) with an average SBP of ≥130 mmHg. • For older adults (≥65 years of age) with hypertension and a higher burden of comorbidity and limited life expectancy, clinical judgment, patient preference, and a team-based approach to assess risk/benefit is reasonable for decisions regarding intensity of BP lowering and choice of antihypertensive drugs. Hypertensive Crises • In adults with a hypertensive emergency, admission to an intensive care unit is recommended for continuous monitoring of BP and target organ damage and for parenteral administration of an appropriate agent. • For adults with a compelling condition (i.e., aortic dissection, severe pre-eclampsia or eclampsia, or pheochromocytoma crisis), SBP should be reduced to <140 mmHg during the first hour and to <120 mmHg in aortic dissection. • For adults without a compelling condition, SBP should be reduced by no more than 25% within the first hours; then, if stable, to 160/100 mmHg within the next two to six hours; and then cautiously to normal during the following 24 to 48 hours. Cognitive Decline and Dementia • In adults with hypertension, BP lowering is reasonable to prevent cognitive decline and dementia. Patients Undergoing Surgical Procedures • In patients with hypertension undergoing major surgery who have been on beta-blockers chronically, beta-blockers should be continued. • In patients with hypertension undergoing planned elective major surgery, it is reasonable to continue medical therapy for hypertension until surgery. • In patients with hypertension undergoing major surgery, discontinuation of ACE inhibitors or ARBs perioperatively may be considered. • In patients with planned elective major surgery and SBP ≥180 mmHg or DBP ≥110 mmHg, deferring surgery may be considered. • For patients undergoing surgery, abrupt pre-operative discontinuation of beta-blockers or clonidine is potentially harmful. • Beta-blockers should not be started on the day of surgery in beta-blocker-naïve patients. • Patients with intraoperative hypertension should be managed with IV medications until such time as oral medications can be resumed.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the central α-agonists are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Central Alpha-Agonists[5-8]

Indication	Single Entity Agents		
	Clonidine	Guanfacine	Methyldopa
Treatment of hypertension	✔ *	✔ *	✔

*Alone or in combination with other antihypertensive agents.
†This fixed combination drug is not indicated for the initial therapy of hypertension.

IV. Pharmacokinetics

The pharmacokinetic parameters of the central α-agonists are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Central Alpha-Agonists[6]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Clonidine	Oral: 75 to 100 TD: 60	20 to 40	Liver	Renal (40 to 60) Feces (22)	Oral: 22 TD: 12 to 13
Guanfacine	80	70	Liver	Renal (50)	17
Methyldopa	25 to 50	Negligible (% not reported)	Liver	Renal (70) Feces (30 to 50)	1.7

TD=transdermal

V. Drug Interactions

Significant drug interactions with the central α-agonists are listed in Table 5.

Table 5. Significant Drug Interactions with the Central Alpha-Agonists[6]

Generic Name(s)	Interaction	Mechanism
Central α-agonists (clonidine)	Beta-adrenergic blockers	The severity of rebound hypertension associated with abrupt withdrawal of clonidine may be greater in patients taking β-adrenergic blockers. This combination has also been reported to cause paradoxical hypertension. The mechanism of this interaction is unknown.
Central α-agonists (clonidine)	Tricyclic antidepressants	The antihypertensive effectiveness of clonidine may be decreased. Tricyclic antidepressants may also worsen the rebound reactions, such as hypertension and tachycardia, from abrupt clonidine withdrawal. The mechanism of this interaction is unknown.
Central α-agonists (clonidine)	Diltiazem, verapamil	Sinus bradycardia, AV block and severe hypotension may occur with coadministration of clonidine and diltiazem/verapamil. The mechanism of this interaction is unknown.
Central α-agonists (guanfacine)	Conivaptan	Concurrent use of conivaptan and guanfacine may result in increased guanfacine exposure due to CYP3A4 inhibition.
Central α-agonists (methyldopa)	Sympathomimetics	The coadministration of methyldopa and sympathomimetics may result in an increased pressor response, possibly resulting in hypertension.
Central α-agonists (methyldopa)	Entacapone	Concurrent use of entacapone and methyldopa may result in an increased risk of tachycardia, hypertension, and arrhythmias.
Central α-agonists (methyldopa)	Monoamine oxidase inhibitors	Metabolites of methyldopa stimulate release of endogenous catecholamines that are usually metabolized by MAOIs, thereby leading to excessive sympathetic stimulation.

VI. Adverse Drug Events

The most common adverse drug events reported with the central α-agonists are listed in Table 6. Abrupt discontinuation may cause nervousness, palpitations, headache, perspiration, nausea, and agitation. In some cases, sudden discontinuation may cause potentially dangerous rebound hypertension.[5,6]

Table 6. Adverse Drug Events (%) Reported with the Central Alpha-Agonists[5-8]

Adverse Events	Single Entity Agents			
	Clonidine Oral	Clonidine Transdermal	Guanfacine	Methyldopa
Cardiovascular				
Angina	-	-	-	✔
Arrhythmia	✔	-	-	-
Atrioventricular block	✔	-	-	-
Bradycardia	✔	-	≤3	✔
Carotid sinus sensitivity	-	-	-	✔
Chest pain	<1	-	≤3	-
Congestive heart failure	✔	-	-	✔
Edema	-	-	-	✔
Electrocardiogram abnormalities	✔	-	-	-
Hypotension	-	-	-	✔
Myocarditis	-	-	-	✔
Orthostatic hypotension	3	-	-	✔
Palpitations	✔	-	≤3	-
Pericarditis	-	-	-	✔
Peripheral edema	-	-	-	>10
Reynaud's phenomenon	✔	-	-	-
Syncope	✔	-	-	<1
Tachycardia	✔	-	-	-
Central Nervous System				
Agitation	✔	-	-	-
Amnesia	-	-	≤3	-
Anxiety	✔	-	-	1 to 10
Bell's palsy	-	-	-	✔
Confusion	-	-	≤3	-
Delirium	✔	-	-	-
Decreased mental acuity	-	-	-	✔
Delusional perception	✔	-	-	✔
Depression	✔	-	≤3	1 to 10
Dizziness	16	2	12 to 15	✔

Adverse Events	Single Entity Agents			
	Clonidine Oral	Clonidine Transdermal	Guanfacine	Methyldopa
Drowsiness	33	12	-	1 to 10
Fatigue	4	6	2 to 10	-
Hallucinations	<1	-	-	-
Headache	1	5	3 to 13	1 to 10
Insomnia	5	2	≤3	-
Involuntary movements	-	-	-	✔
Lightheadedness	-	-	-	✔
Lethargy	-	3	-	-
Nervousness	3	1	-	-
Nightmares	✔	-	-	✔
Paresthesia	✔	-	-	✔
Parkinsonism	-	-	-	✔
Restlessness	✔	-	-	-
Sedation	10	3	-	✔
Sleep disturbances	✔	-	-	-
Somnolence	-	-	5 to 39	-
Weakness	10	-	2 to 7	✔
Dermatological				
Allergic contact sensitization	-	5	-	-
Alopecia	✔	-	-	-
Angioedema	✔	-	-	-
Blanching	-	1	-	-
Burning	-	3	-	-
Contact dermatitis	-	19	-	-
Dermatitis	-	-	≤3	-
Edema	3	3	-	-
Erythema	-	15 to 50	-	-
Excoriation	-	3	-	-
Exfoliative dermatitis	-	-	-	✔
Hives	✔	-	-	-
Hyperpigmentation	-	5	-	-
Lupus-like syndrome	-	-	-	✔
Morbilliform or macro papular eruptions	-	1	-	-
Pruritus	7	15 to 50	≤3	-
Purpura	-	-	≤3	-
Rash	✔	-	-	✔

Adverse Events	Single Entity Agents			
	Clonidine Oral	Clonidine Transdermal	Guanfacine	Methyldopa
Sweating	-	-	≤3	<1
Throbbing	-	3	-	-
Toxic epidermal necrolysis	-	-	-	✔
Urticaria	✔	<1	-	-
Vasculitis	-	-	-	✔
Vesiculation	-	7	-	-
Endocrine and Metabolic				
Breast enlargement	-	-	-	✔
Erectile dysfunction	✔	-	-	-
Gynecomastia	✔	-	-	✔
Hyperprolactinemia	-	-	-	✔
Impotence	3	2	3 to 7	✔
Lactation	-	-	-	✔
Pancreatitis	-	-	-	✔
Sexual dysfunction	3	2	≤3	✔
Sodium retention	-	-	-	<1
Weight gain	✔	-	-	-
Gastrointestinal				
Abdominal Pain	✔	-	≤3	-
Anorexia	1	-	-	-
Colitis	-	-	-	✔
Constipation	10	1	2 to 15	✔
Diarrhea	-	-	≤3	✔
Distention	-	-	-	✔
Dry mouth	40	25	10 to 54	1 to 10
Dry throat	-	2	-	-
Dyspepsia	-	-	≤3	-
Dysphagia	-	-	≤3	-
Flatus	-	-	-	✔
Nausea	5	1	≤3	✔
Pseudo-obstruction	✔	-	-	-
Parotitis	✔	-	-	-
Salivary gland pain	✔	-	-	-
Sialadenitis	-	-	-	✔
Sore tongue	-	-	-	✔
Taste alteration	-	1	≤3	-

Adverse Events	Single Entity Agents			
	Clonidine Oral	Clonidine Transdermal	Guanfacine	Methyldopa
Vomiting	5	-	-	✔
Weight gain	1	-	-	✔
Genitourinary				
Micturition difficulties	✔	-	-	-
Nocturia	✔	-	-	-
Testicular disorder	-	-	≤3	-
Urinary incontinence	-	-	≤3	<1
Urinary retention	1	-	-	-
Hematologic				
Bone marrow depression	-	-	-	✔
Eosinophilia	-	-	-	✔
Granulocytopenia	-	-	-	✔
Hemolytic anemia	-	-	-	✔
Leukopenia	-	-	-	✔
Positive antinuclear antibody test	-	-	-	✔
Positive Rheumatoid factor test	-	-	-	✔
Positive Coombs test	✔	-	-	✔
Thrombocytopenia	✔	-	-	✔
Hepatic				
Cholestasis	-	-	-	<1
Cirrhosis	-	-	-	<1
Hepatitis	✔	-	-	✔
Jaundice	-	-	-	✔
Laboratory Test Abnormalities				
Blood urea nitrogen increased	-	-	-	✔
Creatinine phosphokinase increased	✔	-	-	-
Hyperglycemia	✔	-	-	-
Liver function test abnormalities	✔	-	-	✔
Musculoskeletal				
Arthralgia	-	-	-	✔
Hypokinesia	-	-	≤3	-
Leg cramps	✔	-	≤3	-
Myalgia	✔	-	-	✔
Respiratory				
Dyspnea	-	-	≤3	<1
Rhinitis	-	-	≤3	-

Adverse Events	Single Entity Agents			
	Clonidine Oral	Clonidine Transdermal	Guanfacine	Methyldopa
Other				
Blurred vision	✔	-	-	-
Dry eyes	✔			
Conjunctivitis	-	-	≤3	-
Drug fever	-	-	-	1 to 10
Fever	✔	-	-	-
Iritis	-	-	≤3	-
Malaise	1	-	≤3	-
Nightmares	<1	-	-	-
Paresis	-	-	≤3	-
Paresthesia	-	-	≤3	-
Tinnitus	-	-	≤3	-
Vision disturbance	-	-	≤3	-
Withdrawal syndrome	✔	-	-	-

✔ Percent not specified
- Event not reported

VII. Dosing and Administration

The usual dosing regimens for the central α-agonists are listed in Table 7.

Table 7. Usual Dosing Regimens for the Central Alpha-Agonists[5-8]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Clonidine	Hypertension: Extended-release tablet: initial, 0.17 mg once daily at bedtime; increase dose in increments of 0.09 mg/day at weekly intervals based on response and tolerability; maximum, 0.52 mg/day Tablet: initial, 0.1 mg twice daily; maintenance, 0.1 to 0.6 mg/day in two divided doses; maximum, 2.4 mg/day Transdermal: initial, 0.1 mg patch once weekly; maintenance, 0.1 to 0.3 mg patch once weekly; maximum, two of the 0.3 mg patches once weekly	Safety and effectiveness in pediatric patients have not been established in adequate and well-controlled trials.	Extended-release tablet: 0.17 mg Tablet: 0.1 mg 0.2 mg 0.3 mg Transdermal patch: 0.1 mg/24 hours 0.2 mg/24 hours 0.3 mg/24 hours
Guanfacine	Hypertension: Tablet: initial, 1 mg once daily at bedtime; maintenance, 1 to 2 mg once daily; maximum, 3 mg once daily	Safety and efficacy in children under 12 have not been established.	Tablet: 1 mg 2 mg
Methyldopa	Hypertension: Tablet: initial, 250 mg 2 to 3 times daily; maintenance, 500 to 2,000 mg daily in two divided doses; maximum dose, 3 g daily	There are no well-controlled clinical trials in pediatric patients. Information on dosing in pediatric patients is supported by evidence from published literature regarding the treatment of hypertension in pediatric patients. Hypertension: Tablet: initial, 10 mg/kg/day in 2 to 4 divided doses; maintenance, titrate up or down until adequate response achieved; maximum, 65 mg/kg/day or 3 g daily, whichever is less	Tablet: 250 mg 500 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the central α-agonists are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Central Alpha-Agonists

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Lilja M et al.[17] (1991) Clonidine 0.1 mg tablets BID vs clonidine 0.2 mg transdermal patch QD	DB, DD, PC, RCT, XO Patients with mild to moderate HTN	N=16 12 weeks	Primary: Change from baseline in supine SBP, standing SBP and heart rate Secondary: Difference in primary endpoints between oral and transdermal clonidine	Primary: Clonidine transdermal patch reduced both supine SBP and DBP by 13/7 mm Hg (P<0.01 and P<0.01) and heart rate by 9 bpm (P<0.01). Oral clonidine reduced only supine SPB by 11 mm Hg (P<0.01). In a standing position, clonidine transdermal patch reduced SBP and DBP by 14/9 mm Hg (P<0.01 and P<0.01) and heart rate by 9 bpm (P<0.01). Oral clonidine reduced only standing heart rate by 8 bpm (P<0.05). Secondary: There were no differences reported in primary endpoints between clonidine transdermal patch and oral clonidine (P value not reported).
Houston et al.[18] (1993) Clonidine transdermal 0.1 to 0.3 mg QD plus nifedipine 60 mg QD (single entity products) vs nifedipine 60 mg QD	OL, PC, PRO Male and nonpregnant female patients between 18 and 75 years of age with mild to moderate HTN and inadequate response to nifedipine	N=42 8 weeks	Primary: Change in seated DBP to less than 90 mmHg at 8 weeks Secondary: Not reported	Primary: Patients on combination therapy experienced a reduction of 16/14 mmHg in the mean seated blood pressure vs placebo (P<0.01) with mean seated blood pressure of 127/87 mmHg. A reduction of 5/10 mmHg in the mean seated blood pressure was seen with combination therapy vs nifedipine monotherapy (P<0.01). A reduction of 18/12 mmHg in the mean standing blood pressure was seen with combination therapy vs placebo (P<0.01). A reduction of 9/9 mmHg in the mean standing blood pressure was seen with combination therapy vs nifedipine monotherapy (P<0.01). Secondary: Not reported
Krieger et al.[19] (2018) ReHOT	OL, RCT Patients with resistant	N=162 12 weeks	Primary: BP control (determined by office BP<140/90	Primary: Compared with the spironolactone group, the clonidine group presented similar rates of achieving the primary end point (20.5 vs 20.8%, respectively; RR, 1.01; 95% CI, 0.55 to 1.88; P=1.00).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Clonidine 0.1 mg BID (could be titrated to 0.2 or 0.3 mg BID) vs spironolactone 12.5 mg QD (could be titrated to 25 or 50 mg/ day)	hypertension (no office and ambulatory BP monitoring control, despite treatment with 3 drugs, including a diuretic, for 12 weeks)		and ambulatory 24-hour mean BP <130/80) Secondary: BP control by each evaluation method, absolute BP reduction	Secondary: Secondary end point analysis showed similar office BP (33.3 vs 29.3%) and ambulatory BP monitoring (44 vs 46.2%) control for spironolactone and clonidine, respectively. However, spironolactone promoted greater decrease in 24-hour systolic and diastolic BP and diastolic daytime ambulatory BP than clonidine.
Boyles et al.[20] (1984) Methyldopa 250 to 800 mg/day and HCTZ 25 to 100 mg/day vs HCTZ 25 to 100 mg/day	OL, RCT Patients ≥59 years with isolated systolic HTN	N=21 18 weeks	Primary: Changes in blood pressure from baseline Secondary: Not reported	Primary: At two weeks standing blood pressure fell from a mean of 166/90 mmHg at baseline to 164/88 mmHg with HCTZ monotherapy. At four weeks standing blood pressure fell from a mean of 164/88 mmHg at the end of the two week HCTZ monotherapy period to 145/811 mmHg at two weeks with combination therapy. At 18 weeks standing blood pressure fell from a mean of 166/90 mmHg at baseline to 132/80 mmHg with combination therapy. Secondary: Not reported
Channick et al.[21] (1981) Methyldopa 250 mg/day and HCTZ 15 mg/day vs chlorthalidone 50 mg/day and reserpine 0.25	OL, RCT Patients with HTN	N=56 12 weeks	Primary: Efficacy of blood pressure lowering to goal DBP ≤90 mmHg Secondary: Adverse effects	Primary: Goal DBP of ≤90 mmHg was reached in 91% of the chlorthalidone and reserpine group vs 55% in the methyldopa and HCTZ group (P<0.001). Secondary: The incidence of adverse effects was 31% with chlorthalidone and reserpine vs 64% with methyldopa and HCTZ (P<0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day				
Finnerty et al.[22] (1979) Methyldopa 500 mg to 2,000 mg QD vs reserpine 0.125 mg to 0.25 mg QD vs propranolol 80 mg to 320 mg QD All patients received hydro-flumethiazide* 50 or 100 mg QD.	RCT, SB Patients with HTN unresponsive to hydroflumethiazide monotherapy	N=59 9 weeks	Primary: Percentage of patients achieving a DBP <90 mm Hg Secondary: Not reported	Primary: At trial endpoint, 20 patients (100%) receiving reserpine, 13 of the 19 patients (68.4%) receiving methyldopa and 16 of the 20 patients (80%) receiving propranolol achieved a DBP <90 mm Hg (mean reductions and P values not reported). Secondary: Not reported
Fernandez et al.[23] (1980) Methyldopa 750 mg/day vs chlorothiazide 450 mg/day vs methyldopa and chlorothiazide	DB, PC, RCT, XO Patients with uncomplicated HTN	N=44 4 weeks	Primary: Blood pressure lowering efficacy Secondary: Adverse effects	Primary: No significant differences in supine blood pressure for any treatment compared to placebo was observed (P value not reported). However, upright SBP, DBP and mean blood pressure were significantly lower with methyldopa and methyldopa and chlorothiazide compared to placebo (P<0.05 for all). Secondary: Adverse effects were reported as infrequent (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
250-150 mg/day* (fixed-dose combination product) vs placebo				
Materson et al.[24] (1990) Hydralazine 25, 50 or 100 mg BID vs methyldopa 250, 500 or 1,000 mg BID vs metoprolol 50, 100 or 200 mg BID vs reserpine 0.05, 0.10 or 0.25 mg QD All patients received HCTZ 25 to 100 mg QD.	DB, MC, RCT Men ≥60 years with HTN not currently receiving antihypertensive therapy and DBP 90 to 114 mm Hg and SBP <240 mm Hg or a DBP <100 mm Hg and a SBP <240 mm Hg if currently taking antihypertensive therapy and the blood pressure criteria was met after ≥2 weeks without medication	N=690 12 months	Primary: The average reduction in SBP and DBP, the number of patients achieving the goal blood pressure, the average change in heart rate Secondary: The rates of drug intolerances, adverse effects	Primary: Across all four treatments, there was an additional average reduction in BP of 13.1/10.6 mm Hg. The average reduction in SBP from baseline to endpoint for hydralazine, methyldopa, metoprolol and reserpine were -11.5±10.1 (P<0.001), -15.0±13.7 (P<0.001), -13.0±15.4 (P<0.001) and -12.7±11.5 (P<0.001), respectively. There was no significant difference in SBP reductions among the different treatments (P=0.43). The average reduction in DBP from baseline to endpoint for hydralazine, methyldopa, metoprolol and reserpine were -11.3±5.9 (P<0.001), -10.6±6.3 (P<0.001), -10.6±6.7 (P<0.001) and -9.8±6.3 (P<0.001), respectively. There was no significant difference in DBP reductions among the different treatments (P=0.59). The average change in heart rate from baseline to endpoint for hydralazine, methyldopa, metoprolol and reserpine were 1.4±10.5 (P value not significant), -1.6±9.3 (P value not significant), 15.9±11.9 (P<0.05) and -7.9±10.7 (P<0.05), respectively. There was a significant difference in change in heart rate among the different treatments (P<0.001). The percentage of patients achieving the goal blood pressure at endpoint with hydralazine, methyldopa, metoprolol and reserpine were 85.3, 81.7, 76.9 and 72.3%, respectively (P=0.28). Secondary: Drug intolerance, defined as adverse effects prompting dose reduction or discontinuation, was present in 23.3% of patients not achieving goal blood pressure compared to 2.8% of those who did (P<0.001). This was significant with hydralazine, methyldopa and metoprolol, but not with reserpine.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There were 27 (10%) treatment discontinuations due to adverse effects (hydralazine [n=3], methyldopa [n=8], metoprolol [n=9] and reserpine [n=7]). There were two treatment discontinuations with methyldopa and one with reserpine due to depression. The overall incidence of volunteered moderate or severe adverse effects, not prompting treatment discontinuation, was significantly greater (P<0.01) with methyldopa (31%) and hydralazine (25%) compared to reserpine (15%) or metoprolol (9%).
McAreavey et al.[25] (1984) Hydralazine 12.5 mg QD up to 100 mg BID vs labetalol 200 mg QD up to 1,600 mg BID vs methyldopa 125 mg QD up to 1,000 mg BID vs prazosin 0.5 mg QD up to 10 mg BID vs	DB, PG, RCT Patients with inadequately controlled HTN while receiving atenolol 100 mg/day and bendrofluazide* 5 mg/day	N=238 6 months	Primary: Comparative safety and efficacy, target blood pressure <140/95 mm Hg Secondary: Not reported	Primary: Target blood pressure was reached in 25% of patients receiving hydralazine, 23% of patients receiving minoxidil, 19% of patients receiving prazosin, 17% of patients receiving methyldopa and zero percent of patients receiving placebo (P values not reported). Labetalol had the highest withdrawal rate compared to the other treatments with 78% (P<0.05). Minoxidil had the second highest withdrawal rate with 57% (P<0.05), due to fluid retention. There were no significant differences in withdrawal rates among the other treatments. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo Minoxidil as add on therapy was given to men only. Doses were titrated upward at 2-week intervals until target BP or maximum dose was reached.				

*Agent not available in the United States.
Drug regimen abbreviations: BID=twice daily, QD=once daily
Study design abbreviation: DB=double-blind, DD=double-dummy, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, SB=single blind, XO=cross over
Miscellaneous abbreviations: DBP=diastolic blood pressure, HCTZ=hydrochlorothiazide, HTN=hypertension, SBP=systolic blood pressure

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 10. Relative Cost of the Central Alpha-Agonists

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Clonidine	extended-release tablet, tablet, transdermal patch	N/A	N/A	$
Guanfacine	tablet	N/A	N/A	$
Methyldopa	tablet	N/A	N/A	$

*Generic is available in at least one dosage form or strength.
HCTZ=hydrochlorothiazide, N/A=not available

X. Conclusions

The central alpha-agonists are approved for the treatment of hypertension, and all of the agents are available in a generic formulation.[5-8] There are several national and international organizations that have published guidelines on the treatment of hypertension. Most of the guidelines do not address the use of the central α-agonists.[1,9-16] Thiazide-type diuretics are frequently recommended as initial therapy in patients with uncomplicated hypertension. According to the National Heart, Lung, and Blood Institute's Eighth Report of The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8), thiazide-type diuretics should be utilized first-line for most patients with hypertension, either alone or in combination with another antihypertensive from a different medication class (e.g., ACE inhibitors, ARBs, β-blockers, calcium

channel blockers).[1] Several guidelines consistently recommend that the selection of an antihypertensive agent be based on compelling indications for use.[1,9-16] Methyldopa is safe and effective to use during pregnancy.[10-11]

There are limited head-to-head studies with the central α-agonists. Clinical trials have compared combination therapy to monotherapy. In these studies, the more aggressive treatment regimen lowered systolic and diastolic blood pressure to a greater extent than the less-intensive treatment regimen.[18,20] There does not appear to be any difference in efficacy with the oral or transdermal formulations of clonidine.[17] According to treatment guidelines, most patients will need more than one antihypertensive agent to achieve blood pressure goals.[1,9-16] Certain guidelines note that fixed combination antihypertensive medications can favor compliance and simplify medication regimens.[10] However, there are no prospective, randomized-controlled trials that have demonstrated better clinical outcomes with any central α-agonist fixed-dose combination product compared to the coadministration of the individual components as separate formulations.

The most common adverse events reported with the central α-agonists include dizziness, drowsiness, dry mouth, and somnolence. Abrupt discontinuation may cause nervousness, palpitations, headache, perspiration, nausea, and agitation. In some cases, sudden discontinuation may cause potentially dangerous rebound hypertension.[5-8]

There is insufficient evidence to support that one brand central alpha-agonist is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand central alpha-agonists within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand central alpha-agonist is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Direct Vasodilators
AHFS Class 240820
May 8, 2024

I. Overview

The direct vasodilators are approved for the treatment of heart failure and hypertension.[1-4] Hydralazine and minoxidil interfere with calcium movement within the vascular smooth muscle, which is responsible for initiating and maintaining the contractile state. They exert a peripheral vasodilating effect through a direct relaxation of vascular smooth muscle. This leads to decreased arterial blood pressure, decreased peripheral vascular resistance, as well as an increase in heart rate, stroke volume, and cardiac output. Hydralazine is available as a single entity product, as well as in combination with isosorbide dinitrate. Isosorbide dinitrate enters vascular smooth muscle and is converted to nitric oxide, which results in dilatation of peripheral arteries and veins. Dilation of the veins promotes peripheral pooling of blood and decreases venous return to the heart. Dilation of the arteries reduces systemic vascular resistance, systolic arterial pressure, and mean arterial pressure.[1,2] The exact mechanism of action of the fixed-dose combination product containing isosorbide dinitrate and hydralazine in the treatment of heart failure has not been established.[3]

The direct vasodilators that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All agents are available in a generic formulation. This class was last reviewed in May 2022.

Table 1. Direct Vasodilators Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Hydralazine	injection, tablet	N/A	hydralazine
Minoxidil	tablet	N/A	minoxidil
Nitroprusside	injection^	Nitropress®*, Nipride®	none
Combination Products			
Isosorbide dinitrate and hydralazine	tablet	BiDil®*	none

*Generic is available in at least one dosage form or strength.
^Product is primarily administered in an institution.
PDL=Preferred Drug List
N/A=Not available

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the direct vasodilators are summarized in Table 2.

Table 2. Treatment Guidelines Using the Direct Vasodilators

Clinical Guideline	Recommendations
Eighth Joint National Committee (JNC 8): **2014 Evidence-based Guideline for the Management of High Blood Pressure in Adults (2014)**[5]	• Pharmacologic treatment should be initiated in patients ≥60 years of age to lower blood pressure at systolic blood pressure ≥150 mm Hg or diastolic blood pressure ≥90 mm Hg and to a goal systolic blood pressure <150 mm Hg and goal diastolic blood pressure <90 mm Hg. Adjustment of treatment is not necessary if treatment results in lower blood pressure and treatment is well tolerated and without adverse effects on health or quality of life. • In patients <60 years of age, pharmacologic treatment should be initiated to lower blood pressure at diastolic blood pressure ≥90 mm Hg to a goal diastolic blood pressure <90 mm Hg. • In patients <60 years of age, pharmacologic treatment should be initiated to lower blood pressure at systolic blood pressure ≥150 mm Hg to a goal diastolic blood pressure <140 mm Hg.

Clinical Guideline	Recommendations
	• For patients ≥18 years of age with chronic kidney disease or diabetes, pharmacologic treatment should be initiated to lower blood pressure at systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg and to a goal systolic blood pressure <140 mm Hg and goal diastolic blood pressure <90 mm Hg. • Initial antihypertensive treatment for the general nonblack population, including those with diabetes, should include thiazide-type diuretic, calcium channel blocker (CCB), ACE inhibitor, or ARB. • Initial antihypertensive treatment for the general black population, including those with diabetes, should include thiazide-type diuretic or CCB. • For patients ≥18 years of age with chronic kidney disease regardless of race or diabetes status, initial (or add-on) treatment should include an ACE inhibitor or ARB to improve kidney outcomes. • The main goal of antihypertensive treatment is to attain and maintain goal blood pressure. • If goal blood pressure is not attained within a month of treatment, the dose of the initial drug should be increased or second drug from the thiazide-type diuretic, CCB, ACE inhibitor, or ARB classes should be added. • If goal is not achieved with two drugs, a third drug from the thiazide-type diuretic, CCB, ACE inhibitor, or ARB classes should be added. • An ACE inhibitor and ARB should not be used together. • Antihypertensive classes can be used if the patient is unable to achieve goal blood pressure with three agents or had a contraindication to a preferred class. • If blood pressure is not able to be achieved or in complicated patients, referral to a hypertension specialist may be indicated.
International Society of Hypertension: **Global Hypertension Practice Guidelines (2020)[6]**	<u>Lifestyle modifications</u> • Lifestyle modification is the first line of antihypertensive treatment. • Salt reduction: Reduce salt added when preparing foods, and at the table. Avoid or limit consumption of high salt foods such as soy sauce, fast foods and processed food including breads and cereals high in salt. • Healthy diet: Eating a diet that is rich in whole grains, fruits, vegetables, polyunsaturated fats and dairy products and reducing food high in sugar, saturated fat and trans fats, such as the DASH diet. • Healthy drinks: Moderate consumption of coffee, green and black tea. Other beverages that can be beneficial include karkadé (hibiscus) tea, pomegranate juice, beetroot juice and cocoa. • Moderation of alcohol consumption: The recommended daily limit for alcohol consumptions is 2 standard drinks for men and 1.5 for women (10 g alcohol/standard drink). Avoid binge drinking. • Weight reduction: Body weight control is indicated to avoid obesity. Particularly abdominal obesity should be managed. Ethnic-specific cut-offs for BMI and waist circumference should be used. Alternatively, a waist-to-height ratio <0.5 is recommended for all populations. • Smoking cessation: Smoking is a major risk factor for cardiovascular disease (CVD), COPD and cancer. Smoking cessation and referral to smoking cessation programs are advised. • Regular physical activity: Studies suggest that regular aerobic and resistance exercise may be beneficial for both the prevention and treatment of hypertension. Moderate intensity aerobic exercise (walking, jogging, cycling, yoga, or swimming) for 30 minutes on five to seven days per week Strength training also can help reduce blood pressure. Performance of resistance/strength exercises on two to three days per week. • Reduce stress and induce mindfulness: Stress should be reduced and mindfulness or meditation introduced into the daily routine. • Reduce exposure to air pollution and cold temperature: Evidence from studies

Clinical Guideline	Recommendations
	support a negative effect of air pollution on blood pressure in the long-term. <u>Pharmacological Treatment</u> • Ideal characteristics of drug treatment o Treatments should be evidence-based in relation to morbidity/mortality prevention. o Use a once-daily regimen which provides 24-hour blood pressure control. o Treatment should be affordable and/or cost-effective relative to other agents. o Treatments should be well-tolerated. o Evidence of benefits of use of the medication in populations to which it is to be applied. • General scheme for drug treatment o Lifestyle modification is the first line of antihypertensive treatment. o Grade 1 hypertension (BP 140 to 159/ 90 to 99): Immediate drug treatment in high-risk patients or those with CVD, chronic kidney disease (CKD), diabetes mellitus (DM), or hypertension-mediated organ damage (HMOD). Drug treatment after three to six months of lifestyle intervention if BP still not controlled in low to moderate risk patients. o Grade 2 hypertension (BP ≥160/100): Immediate drug treatment in all patients. • Core drug-treatment strategy o Step 1: Dual low-dose combination (ACE inhibitor or ARB plus dihydropyridine-calcium channel blockers (DHP-CCB)); consider monotherapy in low-risk grade 1 hypertension or in very old (≥80 years) or frail patients; consider ACE/ARB plus thiazide-like diuretic in post-stroke, very elderly, incipient HF, or CCB intolerance; consider ACE/ARB plus DHP-CCB or DHP-CCB plus thiazide-like diuretics in black patients. o Step 2: Dual full-dose combination (ACE inhibitor or ARB plus DHP-CCB); consider monotherapy in low-risk grade 1 hypertension or in very old (≥80 years) or frail patients; consider ACE/ARB plus thiazide-like diuretic in post-stroke, very elderly, incipient HF, or CCB intolerance. o Step 3: Triple combination (ACE/ARB plus DHP-CCB plus thiazide-like diuretic). o Step 4, resistant hypertension: triple combination plus spironolactone or other drug, alternatives include amiloride, doxazosin, eplerenone, clonidine, or β-blocker. Caution with spironolactone or other potassium sparing diuretics when estimated GFR <45 mL/min/1.73m^2 or K+ >4.5 mmol/L. o Consider β-blockers at any treatment step when there is a specific indication for their use, e.g., heart failure, angina, post-MI, atrial fibrillation, or younger women planning pregnancy or pregnant.
Hypertension Canada: **2020 Guidelines for the Prevention, Diagnosis, Risk Assessment, and Treatment of Hypertension in Adults and Children (2020)**[7]	<u>Indications for drug therapy for adults with hypertension without compelling indications for specific agents</u> • Antihypertensive therapy should be prescribed for average diastolic blood pressure (DBP) measurements of ≥100 mmHg or average systolic blood pressure (SBP) measurements of ≥160 mmHg in patients without macrovascular target organ damage or other cardiovascular risk factors. • Antihypertensive therapy should be strongly considered for average DPB readings ≥90 mmHg or for average SBP readings ≥140 mmHg in the presence of macrovascular target organ damage or other independent cardiovascular risk factors.

Clinical Guideline	Recommendations
	• For high-risk patients, aged 50 years or older, with SBP levels ≥130 mmHg, intensive management to target a SBP <120 mmHg should be considered. Patient selection for intensive management is recommended and caution should be taken in certain high-risk groups. <u>Indications for drug therapy for adults with diastolic and with or without systolic hypertension</u> • Initial therapy should be with either monotherapy or single pill combination (SPC). o Recommended monotherapy choices are: ▪ A thiazide/thiazide-like diuretic, with longer-acting diuretics preferred; ▪ A β-blocker (in patients <60 years of age); ▪ An angiotensin-converting enzyme (ACE) inhibitor (in nonblack patients); ▪ An angiotensin receptor blocker (ARB); or ▪ A long-acting calcium channel blocker (CCB). o Recommended SPC choices are those in which an ACE inhibitor is combined with a CCB, ARB with a CCB, or ACE inhibitor or ARB with a diuretic. o Hypokalemia should be avoided in patients treated with thiazide/thiazide-like diuretic monotherapy. • Additional antihypertensive drugs should be used if target BP levels are not achieved with standard-dose monotherapy. Add-on drugs should be chosen from first-line choices. Useful choices include a thiazide/thiazide-like diuretic or CCB with either: ACE inhibitor, ARB, or β-blocker. Caution should be exercised in combining a nondihydropyridine CCB and a β-blocker. The combination of an ACE inhibitor and an ARB is not recommended. • If BP is still not controlled with a combination of two or more first-line agents, or there are adverse effects, other antihypertensive drugs may be added. • Possible reasons for poor response to therapy should be considered. • α-Blockers are not recommended as first-line agents for uncomplicated hypertension; β-blockers are not recommended as first-line therapy for uncomplicated hypertension in patients ≥60 years of age; and ACE inhibitors are not recommended as first-line therapy for uncomplicated hypertension in black patients. However, these agents may be used in patients with certain comorbid conditions or in combination therapy. <u>Indications for drug therapy for adults with isolated systolic hypertension</u> • Initial therapy should be single-agent therapy with a thiazide/thiazide-like diuretic, a long-acting dihydropyridine CCB, or an ARB. If there are adverse effects, another drug from this group should be substituted. Hypokalemia should be avoided in patients treated with thiazide/thiazide-like diuretic monotherapy. • Additional antihypertensive drugs should be used if target BP levels are not achieved with standard-dose monotherapy. Add-on drugs should be chosen from first-line options. • If BP is still not controlled with a combination of two or more first-line agents, or there are adverse effects, other classes of drugs (such as α-blockers, ACE inhibitors, centrally acting agents, or nondihydropyridine CCBs) may be combined or substituted. • Possible reasons for poor response to therapy should be considered. • α-Blockers are not recommended as first-line agents for uncomplicated isolated systolic hypertension; and β-blockers are not recommended as first-line therapy for isolated systolic hypertension in patients ≥60 years of age. However, both agents may be used in patients with certain comorbid conditions or in combination therapy.

Clinical Guideline	Recommendations
	Guidelines for hypertensive patients with coronary artery disease (CAD) • For most hypertensive patients with CAD, an ACE inhibitor or ARB is recommended. • For hypertensive patients with CAD, but without coexisting systolic heart failure, the combination of an ACE inhibitor and ARB is not recommended. • For high-risk hypertensive patients, when combination therapy is being used, choices should be individualized. The combination of an ACE inhibitor and a dihydropyridine CCB is preferable to an ACE inhibitor and a thiazide/thiazide-like diuretic in selected patients. • For patients with stable angina pectoris but without previous heart failure, myocardial infarction, or coronary artery bypass surgery, either a β-blocker or CCB can be used as initial therapy. • Short-acting nifedipine should not be used. • When decreasing SBP to target levels in patients with established CAD (especially if isolated systolic hypertension is present), be cautious when the DBP is ≤60 mmHg because of concerns that myocardial ischemia might be exacerbated, especially in patients with left ventricular hypertrophy (LVH). Guidelines for patients with hypertension who have had a recent myocardial infarction • Initial therapy should include a β-blocker as well as an ACE inhibitor. • An ARB can be used if the patient is intolerant of an ACE inhibitor. • CCBs may be used in patients after myocardial infarction when β-blockers are contraindicated or not effective. Nondihydropyridine CCBs should not be used when there is heart failure, evidenced by pulmonary congestion on examination or radiography. Treatment of hypertension in association with heart failure • In patients with systolic dysfunction (ejection fraction <40%), ACE inhibitors and β-blockers are recommended for initial therapy. Aldosterone antagonists (mineralocorticoid receptor antagonists) may be combined in treatment for patients with a recent cardiovascular hospitalization, acute myocardial infarction, elevated B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide level, or New York Heart Association (NYHA) Class II-IV symptoms. Careful monitoring for hyperkalemia is recommended when combining an aldosterone antagonist with ACE inhibitor or ARB treatment. Other diuretics are recommended as additional therapy if needed. Beyond considerations of BP control, doses of ACE inhibitors or ARBs should be titrated to those reported to be effective in trials unless adverse effects become manifest. • An ARB is recommended if ACE inhibitors are not tolerated. • A combination of hydralazine and isosorbide dinitrate is recommended if ACE inhibitors and ARBs are contraindicated or not tolerated. • For hypertensive patients whose BP is not controlled, an ARB may be combined with an ACE inhibitor and other antihypertensive drug treatment. Careful monitoring should be used if combining an ACE inhibitor and an ARB because of potential adverse effects such as hypotension, hyperkalemia, and worsening renal function. Additional therapies may also include dihydropyridine CCBs. • An angiotensin receptor-neprilysin inhibitor (ARNI) should be used in place of an ACE inhibitor or ARB for patients with HFrEF (<40%) who remain symptomatic despite treatment with appropriate dose of guideline directed HF therapy. Eligible patients must have a serum potassium <5.2 mmol/L, an eGFR ≤30 mL/min/1.73m^2 and close surveillance of serum potassium and creatinine.

Clinical Guideline	Recommendations

	Treatment of hypertension in association with stroke
	• BP management in acute ischemic stroke (onset to 72 hours)
	  o Please refer to Stroke Best Practice recommendations.
	• BP management after acute ischemic stroke
	  o Strong consideration should be given to the initiation of antihypertensive therapy after the acute phase of a stroke or transient ischemic attack.
	  o After the acute phase of a stroke, BP-lowering treatment is recommended to a target of consistently <140/90 mmHg.
	  o Treatment with an ACE inhibitor and thiazide/thiazide-like diuretic combination is preferred.
	  o For patients with stroke, the combination of an ACE inhibitor and ARB is not recommended.
	• BP management in hemorrhagic stroke (onset to 72 hours)
	  o Please refer to Stroke Best Practice recommendations.
	
	Treatment of hypertension in association with LVH
	• Hypertensive patients with LVH should be treated with antihypertensive therapy to decrease the rate of subsequent cardiovascular events.
	• The choice of initial therapy can be influenced by the presence of LVH. Initial therapy can be drug treatment using ACE inhibitors, ARBs, long-acting CCBs, or thiazide/thiazide-like diuretics. Direct arterial vasodilators such as hydralazine or minoxidil should not be used.
	
	Treatment of hypertension in association with nondiabetic chronic kidney disease
	• Individualize BP targets in patients with chronic kidney disease. Consider intensive targets (SBP <120 mmHg) in appropriate patients.
	• For patients with hypertension and proteinuric chronic kidney disease (urinary protein >150 mg per 24 hours or albumin to creatinine ratio >30 mg/mmol), initial therapy should be an ACE inhibitor or an ARB if there is intolerance to ACE inhibitors.
	• In most cases, combination therapy with other antihypertensive agents might be needed to reach target BP levels.
	• The combination of an ACE inhibitor and ARB is not recommended for patients with nonproteinuric chronic kidney disease.
	
	Treatment of hypertension in association with renovascular disease
	• Patients with hypertension attributable to atherosclerotic renal artery stenosis should be primarily medically managed because renal angioplasty and stenting offers no benefit over optimal medical therapy alone.
	• Renal artery angioplasty and stenting for atherosclerotic hemodynamically significant renal artery stenosis could be considered for patients with uncontrolled hypertension resistant to maximally tolerated pharmacotherapy, progressive renal function loss, and acute pulmonary edema.
	• Patients with confirmed renal fibromuscular dysplasia (FMD) should be referred to a hypertension specialist.
	• Renal artery angioplasty without stenting is recommended for treatment of FMD-related renal artery stenosis. Stenting is not recommended unless needed because of a periprocedural dissection. Surgical revascularization should be considered in cases of complex lesions less amendable to angioplasty, stenosis associated with complex aneurysm, and restenosis despite two unsuccessful attempts of angioplasty.
	
	Treatment of hypertension in association with diabetes mellitus
	• Persons with diabetes mellitus should be treated to attain SBP of <130 mmHg and DBP of <80 mmHg.

Clinical Guideline	Recommendations
	• For persons with cardiovascular or kidney disease, including microalbuminuria, or with cardiovascular risk factors in addition to diabetes and hypertension, an ACE inhibitor or an ARB is recommended as initial therapy. • For persons with diabetes and hypertension not included in other guidelines in this section, appropriate choices include (in alphabetical order): ACE inhibitors, ARBs, dihydropyridine CCBs, and thiazide/thiazide-like diuretics. • If target BP levels are not achieved with standard-dose monotherapy, additional antihypertensive therapy should be used. For persons in whom combination therapy with an ACE inhibitor is being considered, a dihydropyridine CCB is preferable to a thiazide/thiazide-like diuretic. <u>Resistant hypertension</u> • Resistant hypertension is defined as BP above target despite three or more BP-lowering drugs at optimal doses preferably including a diuretic (and usually a renin-angiotensin-aldosterone system blocker and a CCB. • Accurate office and out-of-office BP measurement is essential. • Other reasons for apparent resistant hypertension should be eliminated before diagnosing true resistant hypertension, including nonadherence, white coat effect, and secondary hypertension. • Pharmacotherapy with the additional use of spironolactone, bisoprolol, doxazosin, amiloride, eplerenone, or clonidine with the baseline regimen decreases BP significantly, with the greatest BP-lowering shown with spironolactone. • Patients with resistant hypertension should be referred to providers with expertise in diagnosis and management of hypertension. <u>Hypertension and pediatrics</u> • BP should be measured regularly in children three years of age or older; the auscultatory method is the gold-standard at present. • Initial therapy should be monotherapy, with an ACE inhibitor or ARB (not first-line in black children), or a long-acting dihydropyridine CCB. • The treatment t goal is systolic and diastolic office BP and/or ABPM < 95th percentile or <90th percentile in children with risk factors or target organ damage. • Complex cases should be referred to an expert in pediatric hypertension. <u>Hypertension and pregnancy</u> • Up to 7% of pregnancies are complicated by a hypertensive disorder of pregnancy, and approximately 5% of women will have chronic hypertension when they become pregnant. • The prevalence of hypertension in pregnancy is expected to increase with women becoming pregnant later in their reproductive years and the increasing prevalence of cardiovascular comorbidities such as increased preconception body mass index and maternal diabetes. • The possibility of pregnancy should be considered when managing women with hypertension who are of reproductive age. • Preconception counselling should be offered to all women with hypertension who are considering pregnancy. • ACE inhibitor and ARB therapy should be avoided before conception and during pregnancy unless there is a compelling indication for their use (i.e., proteinuric kidney disease). • Hypertension during pregnancy can increase the risk of adverse maternal and fetal outcomes, including an increased risk of preeclampsia, placental abruption, prematurity, small for gestational age infants, stillbirth, and maternal renal and retinal injury, thus generally requires involvement of an interdisciplinary team

Clinical Guideline	Recommendations
	including obstetrical care providers. • Antihypertensive therapy is recommended for average SBP measurements of ≥140 mmHg or DBP measurements of ≥90 mmHg in pregnant women with chronic hypertension, gestational hypertension, or preeclampsia. Initial antihypertensive therapy should be monotherapy from the following first-line drugs: oral labetalol, oral methyldopa, long-acting oral nifedipine, or other oral b-blockers (acebutolol, metoprolol, pindolol, and propranolol). Other antihypertensive drugs can be considered as second-line drugs including: clonidine, hydralazine, and thiazide diuretics. • Women with severe hypertension with SBP ≥160 mmHg or DBP ≥110 mmHg in pregnancy or postpartum require urgent antihypertensive therapy because it is considered an obstetrical emergency. • Antihypertensive drugs used in breastfeeding women include: labetalol, methyldopa, long-acting nifedipine, enalapril, or captopril.
European Society of Hypertension: **2023 Guidelines for the management of arterial hypertension (2023)**[8]	General recommendations for antihypertensive drug treatment • BP lowering should be prioritized over the selection of specific antihypertensive drug classes because treatment benefit largely originates from BP reduction. • Five major drug classes including, ACE inhibitors, ARBs, β-blockers, CCBs, and Thiazide/Thiazide-like diuretics have effectively reduced blood pressure and cardiovascular events in randomized controlled trials. These drugs and their combinations are recommended as the basis of antihypertensive treatment strategies. • Initiation of therapy with a two-drug combination is recommended for most hypertensive patients. Preferred combinations should comprise a RAS blocker (either an ACE inhibitor or an ARB) with a CCB or thiazide/thiazide-like diuretic. Other combinations of the five major drug classes can be used. • Initiation with monotherapy can be considered in patients with: grade 1 hypertension and low-risk if BP is only marginally elevated (less than 150 mmHg SBP and 95 mmHg DBP) high-normal BP and very high cardiovascular risk, frailty and/or and advance age. • If BP is not controlled with the initial two-drug combination by using the maximum recommended and tolerated dose of the respective components, treatment should be increased to a three-drug combination, usually a RAS blocker plus CCB plus thiazide/thiazide-like diuretic. • If BP is not controlled with a three-drug combination by using the maximum recommended and tolerated dose of the respective components, it is recommended to extend treatment according to the recommendations for resistant hypertension. • The use of single pill combinations should be preferred at any treatment step (i.e. during initiation of therapy with a two-drug combination and at any other step of treatment). • β-blocker should be used at initiation of therapy or at any treatment step as guideline-directed medical therapy (e.g., heart failure with reduced ejection fraction, anti-ischemic therapy in chronic coronary syndromes, heart rate control in atrial fibrillation). • β-blockers can be considered in the presence of several other conditions in which their use can be favorable. • The combination of two RAS blockers is not recommended due to increased risk of adverse events, in particular AKI. True-resistant hypertension • In resistant hypertension, it is recommended to reinforce lifestyle measures. • Drugs that can be considered as additional therapy in patients with resistant hypertension are preferably spironolactone (or other MRA), or β-blocker or Alpha-1 blockers or centrally acting agents (clonidine), or amiloride.

Clinical Guideline	Recommendations
	• Thiazide/thiazide-like diuretics are recommended in resistant hypertension if estimated eGFR is ≥30 mL/min/1.73m^2. • Loop diuretics may be considered in patients with an estimated eGFR < 45 mL/min/1.73m^2 and should be used if eGFR falls below 30 mL/min/1.73m^2. • Chlorthalidone (12.5 to 25 mg once daily) could be used with or without a loop diuretic if eGFR is <30 mL/min/1.73m^2. • Renal deprivation can be considered as an additional treatment option in patients with resistant hypertension if eGFR is >40 mL/min/1.73m^2. • Patients with resistant hypertension should be followed very closely. Follow-up includes periodical ambulatory blood pressure monitoring and assessment of hypertension-mediated organ damage, particularly kidney function and serum potassium levels. Regular use of home blood pressure monitoring and monitoring of drug adherence are desirable.
National Institute for Health and Clinical Excellence: **Hypertension in adults: diagnosis and management (2019)**[9]	<u>Choosing antihypertensive drug treatment (for people with or without type II diabetes)</u> • Where possible, recommend treatment with drugs taken only once a day. • Prescribe non-proprietary drugs where these are appropriate and minimize cost. • Offer people with isolated systolic hypertension (systolic blood pressure ≥160 mmHg) the same treatment as people with both raised systolic and diastolic blood pressure. • Offer antihypertensive drug treatment to women of child-bearing potential with diagnosed hypertension in line with recommendations in this guideline. For women considering pregnancy or who are pregnant or breastfeeding, manage hypertension in line with the recommendations on Management of pregnancy with chronic hypertension and Breastfeeding in 'Hypertension in pregnancy'. • When choosing antihypertensive drug treatment for adults of black African or African-Caribbean family origin, consider an angiotensin II receptor blocker, in preference to an angiotensin-converting enzyme inhibitor. <u>Step one treatment</u> • Patients <55 years of age should be offered a step one antihypertensive with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). • Offer an ACE inhibitor or an ARB to adults starting step 1 antihypertensive treatment who have type II diabetes and are of any age or family origin or those aged <55 years but not of black African or African-Caribbean family origin. • If an ACE inhibitor is not tolerated, offer an ARB. • Do not combine an ACE inhibitor with an ARB for the treatment of hypertension. • Offer a calcium channel blocker (CCB) to adults starting step 1 antihypertensive treatment who are >55 years of age and do not have diabetes and are of black African or African-Caribbean family origin and do not have type II diabetes and of any age. • If a CCB is not suitable, for example because of edema or intolerance, or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic. • If diuretic treatment is to be initiated or changed, offer a thiazide‑like diuretic, such as indapamide in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide. • For adults with hypertension who are already receiving treatment with bendroflumethiazide or hydrochlorothiazide, who have stable, well-controlled blood pressure, continue with their treatment. <u>Step two treatment</u>

Clinical Guideline	Recommendations
	• Before considering next step treatment for hypertension discuss with the person if they are taking their medicine as prescribed and support adherence in line with NICE's guideline on "Medicines adherence: involving patients decisions about prescribed medicines and supporting adherence". • If hypertension is not controlled with a step one treatment of an ACE inhibitor or ARB, offer choice of one of the following drugs in addition to the step one treatment: a CCB or a thiazide-like diuretic. • If hypertension is not controlled in adults taking step one treatment of a CCB, offer the choice of one of the following drugs in addition to the step one treatment: an ACE inhibitor or an ARB or a thiazide-like diuretic. • If hypertension is not controlled in adults of black African or African–Caribbean family origin who do not have type 2 diabetes taking step one treatment, consider an ARB, in preference to an ACE inhibitor, in addition to step one treatment. <u>Step three treatment</u> • Before considering step three treatment, review the person's medications to ensure they are being taken at the optimal doses and discuss adherence (see recommendation under step two). • If hypertension is not controlled in adults taking step two treatment, offer a combination of an ACE inhibitor or ARB and a CCB and a thiazide-like diuretic. <u>Step four treatment</u> • If hypertension is not controlled in adults taking the optimal tolerated doses of an ACE inhibitor or an ARB plus a CCB and a thiazide-like diuretic, regard them as having resistant hypertension. • Before considering further treatment for a person with resistant hypertension, confirm elevated clinic blood pressure measurements using ambulatory or home blood pressure recordings, assess for postural hypotension, and discuss adherence. • For people with confirmed resistant hypertension, consider adding a fourth antihypertensive drug as step four treatment or seeking specialist advice. • Consider further diuretic therapy with low-dose spironolactone for adults with resistant hypertension starting step four treatment who have a blood potassium level of 4.5 mmol/l or less. Use particular caution in people with a reduced estimated glomerular filtration rate because they have an increased risk of hyperkalemia. • When using further diuretic therapy for step four treatment of resistant hypertension, monitor blood sodium and potassium and renal function within one month of starting treatment and repeat as needed thereafter. • Consider an alpha-blocker or beta-blocker for adults with resistant hypertension starting step four treatment who have a blood potassium level of more than 4.5 mmol/l. • If blood pressure remains uncontrolled in people with resistant hypertension taking the optimal tolerated doses of four drugs, seek specialist advice.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in Blacks (2010)[10]**	• To attain and maintain blood pressure (BP) below target levels, multiple antihypertensive drugs will be required in most hypertensive blacks. • Use of two-drug combination therapy when SBP is >15 mm Hg and/or DBP is >10 mm Hg above goal levels is increasingly recommended as first-line therapy. • Two-drug regimens have generally contained a thiazide-type diuretic; however, the combination of a calcium channel blocker (CCB) with either an ACE inhibitor or an ARB has been shown equally efficacious in BP lowering but

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	with demonstrated superiority (CCB+ACE) for hard clinical outcomes compared with the same ACE inhibitor plus a thiazide-type diuretic. • In secondary prevention patients, the combination therapy should include a drug(s) with the appropriate compelling indications. • Certain classes of antihypertensive medications, specifically diuretics and CCBs, lower BP on average more than β-blockers and renin-angiotensin system (RAS) blockers in black patients when used as monotherapies. • In the absence of compelling indications, when BP is near goal levels, monotherapy with a diuretic or a CCB is preferred. • Lifestyle modifications should be initiated in all patients with hypertension, whether or not pharmacotherapy is planned. • ACE inhibitors or ARBs are recommended as alternative monotherapy options in the treatment of hypertension in blacks. The rationale for their lower tier monotherapy recommendation is because they have consistently achieved lesser average reductions in BP relative to that observed with monotherapy using either a diuretic or CCB.
Kidney Disease Improving Clinical Outcomes Group: **KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease (2021)**[11]	<u>Blood pressure measurement</u> • The Work Group recommends standardized office blood pressure (BP) measurement in preference to routine office BP measurements for the management of high BP in adults. • The Work Group suggests that out-of-office BP measurements with ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM) be used to complement standardized office BP readings for the management of high BP. <u>Lifestyle interventions for lowering BP in patients with chronic kidney disease (CKD) not receiving dialysis</u> • The Work Group suggests targeting a sodium intake <2 grams of sodium per day (or <90 mmol of sodium per day, or <5 grams of sodium chloride per day) in patients with high BP and CKD. • The Work Group suggests that patients with high BP and CKD be advised to undertake moderate-intensity physical activity for a cumulative duration of at least 150 minutes per week, or to a level compatible with their cardiovascular and physical tolerance. <u>BP management in patients with CKD, with or without diabetes, not receiving dialysis</u> • The Work Group suggests that adults with high BP and CKD be treated with a target systolic BP (SBP) of <120 mmHg, when tolerated, using standardized office BP measurement. • The Work Group recommends starting renin-angiotensin-system inhibitors (RASi) (angiotensin-converting enzyme inhibitor [ACEi] or angiotensin II receptor blocker [ARB]) for people with high BP, CKD, and severely increased albuminuria without diabetes. • The Work Group suggests starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately increased albuminuria without diabetes. • The Work Group recommends starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately-to-severely increased albuminuria with diabetes. • The Work Group recommends avoiding any combination of ACEi, ARB, and direct renin inhibitor (DRI) therapy in patients with CKD, with or without diabetes. <u>BP management in kidney transplant recipients</u> • Treat adult kidney transplant recipients with high BP to a target BP of <130 mmHg systolic and <80 mmHg diastolic using standardized office BP measurement.

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	• The Work Group recommends that a dihydropyridine calcium channel blocker (CCB) or an ARB be used as the first-line antihypertensive agent in adult kidney transplant recipients. BP management in children with CKD • The Work Group suggests that in children with CKD, 24-hour mean arterial pressure by ABPM should be lowered to <50th percentile for age, sex, and height.
American Diabetes Association: **Standards of Medical Care in Diabetes (2023)**[12]	Hypertension/blood pressure control • Blood pressure should be measured at every routine visit. When possible, patients found to have elevated blood pressure (systolic blood pressure 120 to 129 mmHg and diastolic <80 mmHg) should have blood pressure confirmed using multiple readings, including measurements on a separate day, to diagnose hypertension. Patients with blood pressure ≥180/110 and cardiovascular disease could be diagnosed with hypertension at a single visit. • All hypertensive patients with diabetes should monitor their blood pressure at home. • For patients with diabetes and hypertension, blood pressure targets should be individualized through a shared decision-making process that addresses cardiovascular risk, potential adverse effects of antihypertensive medications, and patient preferences. • Individuals with diabetes and hypertension qualify for antihypertensive drug therapy when the blood pressure is persistently elevated ≥130/80 mmHg. The on-treatment target blood pressure goal is <130/80 mmHg, if it can be safely attained. • In pregnant patients with diabetes and preexisting hypertension, a blood pressure target of 110 to 135/85 is suggested in the interest of reducing the risk for accelerated maternal hypertension and minimizing impaired fetal growth. • For patients with blood pressure >120/80, lifestyle intervention consists of weight loss when indicated, a Dietary Approaches to Stop Hypertension (DASH)-style eating pattern including reducing sodium and increasing potassium intake, moderation of alcohol intake, and increased physical activity. • Patients with confirmed office-based blood pressure ≥130/80 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of pharmacologic therapy to achieve blood pressure goals. • Patients with confirmed office-based blood pressure ≥160/100 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of two drugs or a single pill combination of drugs demonstrated to reduce cardiovascular events in patients with diabetes. • Treatment for hypertension should include drug classes demonstrated to reduce cardiovascular events in patients with diabetes (ACE inhibitors, angiotensin receptor blockers, thiazide-like diuretics, or dihydropyridine calcium channel blockers). ACE inhibitors or angiotensin receptor blockers are recommended first-line therapy for hypertension in people with diabetes and coronary artery disease. • Multiple-drug therapy is generally required to achieve blood pressure targets (but not a combination of ACE inhibitors and angiotensin receptor blockers). • An ACE inhibitor or angiotensin receptor blocker, at the maximum tolerated dose indicated for blood pressure treatment, is the recommended first-line treatment for hypertension in patients with diabetes and urinary albumin–to–creatinine ratio ≥300 mg/g creatinine or 30 to 299 mg/g creatinine. If one class is not tolerated, the other should be substituted. • For patients treated with an ACE inhibitor, angiotensin receptor blocker, or diuretic, serum creatinine/estimated glomerular filtration rate and serum potassium levels should be monitored at least annually.

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	• Patients with hypertension who are not meeting blood pressure targets on three classes of antihypertensive medications (including a diuretic) should be considered for mineralocorticoid receptor antagonist therapy. Chronic kidney disease • At least once a year, assess urinary albumin (e.g., spot urinary albumin–to–creatinine ratio) and estimated glomerular filtration rate in patients with type 1 diabetes with duration of five or more years and in all patients with type 2 diabetes. • In people with established diabetic kidney disease, urinary albumin (e.g., spot urinary albumin-to-creatinine ratio) and estimated glomerular filtration rate should be monitored one to four times per year depending on the stage of the disease. Optimize glucose control to reduce the risk or slow the progression of chronic kidney disease (CKD). • For patients with type 2 diabetes and diabetic kidney disease, use of a sodium-glucose cotransporter 2 inhibitor in patients with an estimated glomerular filtration rate ≥20 mL/min/1.73 m^2 and urinary albumin ≥200 mg/g creatinine is recommended to reduce CKD progression and cardiovascular events. • For patients with type 2 diabetes and diabetic kidney disease, use of a sodium–glucose cotransporter 2 inhibitor is recommended to reduce chronic kidney disease progression and cardiovascular events in patients with an estimated glomerular filtration rate ≥20 mL/min/1.73 m^2 and urinary albumin ranging from normal to 200 mg/g creatinine. • In people with type 2 diabetes and diabetic kidney disease, consider use of sodium–glucose cotransporter 2 inhibitors (if estimated glomerular filtration rate is ≥20 mL/min/1.73 m^2), a glucagon-like peptide 1 agonist, or a nonsteroidal mineralocorticoid receptor antagonist (if estimated glomerular filtration rate is ≥25 mL/min/1.73 m^2) additionally for cardiovascular risk reduction. • In people with chronic kidney disease and albuminuria who are at increased risk for cardiovascular events or chronic kidney disease progression, a nonsteroidal mineralocorticoid receptor antagonist shown to be effective in clinical trials is recommended to reduce chronic kidney disease progression and cardiovascular events. • Optimize blood pressure control and reduce blood pressure variability to reduce the risk or slow the progression of CKD. • Do not discontinue renin-angiotensin system blockade for minor increases in serum creatinine (≤30%) in the absence of volume depletion. • For people with nondialysis-dependent stage 3 or higher CKD, dietary protein intake should be a maximum of 0.8 g/kg body weight per day (the recommended daily allowance). For patients on dialysis, higher levels of dietary protein intake should be considered, since protein energy wasting is a major problem in some dialysis patients. • In nonpregnant patients with diabetes and hypertension, either an ACE inhibitor or an angiotensin receptor blocker is recommended for those with modestly elevated urinary albumin–to–creatinine ratio (30 to 299 mg/g creatinine) and is strongly recommended for those with urinary albumin–to–creatinine ratio ≥300 mg/g creatinine and/or estimated glomerular filtration rate <60 mL/min/1.73 m^2. • Periodically monitor serum creatinine and potassium levels for the development of increased creatinine and hyperkalemia when ACE inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists are used, or hypokalemia when diuretics are used. • An ACE inhibitor or an angiotensin receptor blocker is not recommended for the primary prevention of CKD in patients with diabetes who have normal blood pressure, normal urinary albumin–to–creatinine ratio (<30 mg/g creatinine), and

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	normal estimated glomerular filtration rate. • Patients should be referred for evaluation by a nephrologist if they have continuously increasing urinary albumin levels and/or continuously decreasing estimated glomerular filtration rate and an estimated glomerular filtration rate <30 mL/min/1.73 m^2. • Promptly refer to a nephrologist for uncertainty about the etiology of kidney disease, difficult management issues, and rapidly progressing kidney disease.
American College of Cardiology/American Heart Association Task Force: **Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults (2017)**[13]	<u>Initiation of Blood Pressure (BP) Treatment for Overall Cardiovascular Disease (CVD) Risk</u> • Use of BP-lowering medications is recommended for secondary prevention of recurrent CVD events in patients with clinical CVD and an average systolic blood pressure (SBP) ≥130 mmHg or an average diastolic blood pressure (DBP) of ≥80 mmHg and for primary prevention in adults with an estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk of ≥10% and an average SBP of ≥130 mmHg or an average ≥80 mmHg. • Use of BP-lowering medication is recommended for primary prevention of CVD in adults with no history of CVD and with an estimated 10-year ASCVD risk <10% and an SBP of ≥140 mmHg or a DBP of ≥90 mmHg. • Simultaneous use of an angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), and/or renin inhibitor is potentially harmful and is not recommended to treat adults with hypertension. • For adults with confirmed hypertension and known CVD or 10-year ASCVD risk of ≥10%, a BP target <130/80 mmHg is recommended. For adults with confirmed hypertension without additional markers of increased CVD risk, a BP target <130/80 mmHg may be reasonable. • For initiation of antihypertensive drug therapy, first-line agents include thiazide diuretics, calcium channel blockers (CCBs), and ACE inhibitors or ARBs. • Initiation of antihypertensive drug therapy with two first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended in adults with stage 2 hypertension and an average BP >20/10 mmHg above their BP target. • Initiation of antihypertensive drug therapy with a single antihypertensive drug is reasonable in adults with stage 1 hypertension and BP goal <130/80 mmHg with dosage titration and sequential addition of other agents to achieve the BP target. <u>Stable Ischemic Heart Disease (SIHD)</u> • In adults with SIHD and hypertension, a BP target <130/80 is recommended. • Adults with SIHD and hypertension (BP ≥130/80 mmHg) should be treated with medications [e.g., guideline-directed medical therapy (GDMT) beta-blockers, ACE inhibitors, or ARBs] for compelling indications [e.g., previous myocardial infarction (MI), stable angina] as first-line therapy, with the addition of other drugs (e.g., dihydropyridine CCBs, thiazide diuretics, and/or mineralocorticoid receptor antagonists) as needed to further control hypertension. • In adults with SIHD with angina and persistent uncontrolled hypertension, the addition of dihydropyridine CCBs to GDMT beta-blockers is recommended. • In adults who have had a MI or acute coronary syndrome, it is reasonable to continue GDMT beta-blockers beyond three years as long-term therapy for hypertension. • Beta-blockers and/or CCBs might be considered to control hypertension in patients with coronary artery disease (CAD) had an MI more than three years ago and have angina. <u>Heart Failure</u>

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	• In adults with increased risk of HF, the optimal BP in those with hypertension should be <130 mmHg. • Adults with HFrEF and hypertension should be prescribed GDMT titrated to attain a BP <130/80 mmHg. • Non-dihydropyridine CCBs are not recommended in the treatment of hypertension in adults with HFrEF. • In adults with HFpEF who present with symptoms of volume overload, diuretics should be prescribed to control hypertension. • Adults with HFpEF and persistent hypertension after management of volume overload should be prescribed ACE inhibitors or ARBs and beta-blockers titrated to attain SBP <130 mmHg. CKD • Adults with hypertension and CKD should be treated to a BP goal <130/80 mmHg. • In adults with hypertension and CKD [stage 3 or higher or stage 1 or 2 with albuminuria (≥300 mg/d, or ≥300 mg/g albumin-to-creatinine ratio or the equivalent in the first morning void)], treatment with an ACE inhibitor is reasonable to slow kidney disease progression. Treatment with an ARB may be reasonable if an ACE inhibitor is not tolerated. • After kidney transplantation, it is reasonable to treat patients with hypertension to a BP goal <130/80 mmHg and with a CCB on the basis of improved glomerular filtration rate (GFR) and kidney survival. Cerebrovascular Disease • In adults with intracerebral hemorrhage (ICH) who present with SBP >220 mmHg, it is reasonable to use continuous intravenous (IV) drug infusion and close BP monitoring to lower levels. Immediate lowering of SBP to <140 mmHg in adults with spontaneous ICH who present within six hours of the acute event and have an SBP between 150 mmHg and 220 mmHg is not of benefit to reduce death or severe disability and can be potentially harmful. • Adults with acute ischemic stroke and elevated BP who are eligible for treatment with IV tissue plasminogen activator (tPA) should have their BP slowly lowered to <185/110 mmHg before thrombolytic therapy is initiated. • In adults with an acute ischemic stroke, BP should be <185/110 mmHg before administration of IV tPA and should be maintained below 180/105 mmHg for at least the first 24 hours after initiation drug therapy. • Starting or restarting antihypertensive therapy during hospitalization in patients with BP >140/90 mmHg who are neurologically stable is safe and reasonable to improve long-term BP control, unless contraindicated. • In patient with BP ≥220/120 mmHg who did not receive IV alteplase or endovascular treatment and have no comorbid conditions requiring acute antihypertensive treatment, the benefit of initiating or reinitiating treatment of hypertension within the first 48 to 72 hours is uncertain. It might be reasonable to lower BP by 15% during the first 24 hours after onset of stroke. In patients with BP <220/120 mmHg with the same conditions, initiating or reinitiating treatment of hypertension within the first 48 to 72 hours after an acute ischemic stroke is not effective to prevent death or dependency. • Adults with previously treated stroke or transient ischemic attack should be restarted on antihypertensive treatment after the first few days of the index event to reduce the risk of recurrent stroke and other vascular events. Treatment with a thiazide diuretic, ACE inhibitor, or ARB, or combination treatment consisting of a thiazide diuretic plus ACE inhibitor, is useful. • Adults not previously treated for hypertension who experienced a stroke or transient ischemic attack and have an established BP ≥140/90 mmHg should be

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	prescribed antihypertensive treatment a few days after the index event to reduce the risk of recurrent stroke and other vascular event. • For adults who experience a stroke or transient ischemic attack, selection of specific drugs should be individualized on the basis of patient comorbidities and agent pharmacological class. • For adults who experience a stroke or transient ischemic attack, a BP goal <130/80 mmHg may be reasonable. • For adults with a lacunar stroke, a target SBP goal <130 mmHg may be reasonable. • In adults previously untreated for hypertension who experience an ischemic stroke or transient ischemic attack and have an SBP <140 mmHg and a DBP <90 mmHg, the usefulness of initiating antihypertensive treatment is not well established. <u>Peripheral Artery Disease (PAD)</u> • Adults with hypertension and PAD should be treated similarly to patients with hypertension without PAD. <u>Diabetes Mellitus (DM)</u> • In adults with DM and hypertension, antihypertensive drug treatment should be initiated at a BP of ≥130/80 mmHg with a treatment goal <130/80 mmHg. • In adults with DM and hypertension, all first-line classes of antihypertensive agents (i.e., diuretics, ACE inhibitors, ARBs, and CCBs) are useful and effective. • In adults with DM and hypertension, ACE inhibitors or ARBs may be considered in the presence of albuminuria. <u>Atrial Fibrillation, Valvular Heart Disease, and Aortic disease</u> • Treatment of hypertension can be useful for prevention of recurrence of AF. • In adults with asymptomatic aortic stenosis, hypertension should be treated with pharmacotherapy, starting at a low dose and gradually titrating upward as needed. • In patients with chronic aortic insufficiency, treatment of systolic hypertension with agents that do not slow the heart rate (i.e., avoid beta-blockers) is reasonable. • Beta-blockers are recommended as the preferred antihypertensive agents in patients with hypertension and thoracic aortic disease. <u>Racial and Ethnic Differences in Treatment</u> • In black adults with hypertension but without HF or CKD, including those with DM, initial antihypertensive treatment should include a thiazide-type diuretic or CCB. Two or more antihypertensive medications are recommended to achieve a BP target <130/80 mmHg in most adults with hypertension, especially in black adults with hypertension. <u>Pregnancy</u> • Women with hypertension who become pregnant, or are planning to become pregnant, should be transitioned to methyldopa, nifedipine, and/or labetalol during pregnancy. • Women with hypertension who become pregnant should not be treated with ACE inhibitors, ARBs, or direct renin inhibitors. <u>Older Persons</u> • Treatment of hypertension with an SBP treatment goal <130 mmHg is recommended for noninstitutionalized ambulatory community-dwelling adults

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	(≥65 years of age) with an average SBP of ≥130 mmHg. • For older adults (≥65 years of age) with hypertension and a higher burden of comorbidity and limited life expectancy, clinical judgment, patient preference, and a team-based approach to assess risk/benefit is reasonable for decisions regarding intensity of BP lowering and choice of antihypertensive drugs. Hypertensive Crises • In adults with a hypertensive emergency, admission to an intensive care unit is recommended for continuous monitoring of BP and target organ damage and for parenteral administration of an appropriate agent. • For adults with a compelling condition (i.e., aortic dissection, severe pre-eclampsia or eclampsia, or pheochromocytoma crisis), SBP should be reduced to <140 mmHg during the first hour and to <120 mmHg in aortic dissection. • For adults without a compelling condition, SBP should be reduced by no more than 25% within the first hours; then, if stable, to 160/100 mmHg within the next two to six hours; and then cautiously to normal during the following 24 to 48 hours. Cognitive Decline and Dementia • In adults with hypertension, BP lowering is reasonable to prevent cognitive decline and dementia. Patients Undergoing Surgical Procedures • In patients with hypertension undergoing major surgery who have been on beta-blockers chronically, beta-blockers should be continued. • In patients with hypertension undergoing planned elective major surgery, it is reasonable to continue medical therapy for hypertension until surgery. • In patients with hypertension undergoing major surgery, discontinuation of ACE inhibitors or ARBs perioperatively may be considered. • In patients with planned elective major surgery and SBP ≥180 mmHg or DBP ≥110 mmHg, deferring surgery may be considered. • For patients undergoing surgery, abrupt pre-operative discontinuation of beta-blockers or clonidine is potentially harmful. • Beta-blockers should not be started on the day of surgery in beta-blocker-naïve patients. • Patients with intraoperative hypertension should be managed with IV medications until such time as oral medications can be resumed.
American Heart Association/American College of Cardiology/ Heart Failure Society of America: **2022 AHA/ACC /HFSA Guideline for the Management of Heart Failure (2022)[14]**	Treatment of Stage A heart failure (HF) • Hypertension should be controlled in accordance with guideline-directed medication therapy for hypertension to prevent symptomatic HF. (LoE: A) • In patients with type 2 diabetes and either established CVD or at high cardiovascular risk, SGLT-2 inhibitors should be used to prevent hospitalizations for HF. (LoE: A) • In the general population, healthy lifestyle habits such as regular physical activity, maintaining normal weight, healthy dietary patterns, and avoiding smoking are helpful to reduce future risk of HF. (LoE: B) • Patients at risk of developing HF, natriuretic peptide biomarker-based screening followed by team-based care, including a cardiovascular specialist optimizing therapy, can be useful to prevent the development of LV dysfunction (systolic or diastolic) or new-onset HF. (LoE: B) Treatment of Stage B heart failure • In patients with LVEF≤40%, ACE inhibitors should be used to prevent HF and reduce mortality. (LoE: A) • In patients with a recent or remote history of MI or ACS, statins should be used

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	to prevent symptomatic HF and adverse cardiovascular events. (LoE: A) • In patients with a recent MI and LVEF≤40% who are intolerant to ACE inhibitors, ARB should be used to prevent symptomatic HF and reduce mortality. (LoE: B) • In patients with a recent or remote history of MI or ACS and LVEF≤40%, evidence-based beta blockers should be used to reduce mortality. (LoE: B) • In patients who are at least 40 days post-MI with LVEF ≤30% and NYHA class I symptoms while receiving guideline-directed medication therapy and have reasonable expectation of meaningful survival for greater than one year, an implantable cardioverter-defibrillator is recommended for primary prevention of sudden cardiac death to reduce total mortality. (LoE: B) • In patients with LVEF ≤40%, beta blockers should be used to prevent symptomatic HF. (LoE: C) • In patients with LVEF ≤50%, thiazolidinediones should not be used because they increase the risk of HF, including hospitalizations. (LoE: B) • In patients with LVEF ≤50%, nondihydropyridine calcium channel blockers with negative inotropic effects may be harmful. (LoE: C) <u>Treatment for Stage C Heart Failure with Reduced Ejection Fraction (HFrEF)</u> • For patients with stage C HF, avoiding excessive sodium intake is reasonable to reduce congestive symptoms. (LoE: C) • In patients with HF who have fluid retention, diuretics are recommended to relieve congestion, improve symptoms, and prevent worsening HF. (LoE: B) • For patients with HF and congestive symptoms, addition of a thiazide (e.g., metolazone) to treatment with a loop diuretic should be reserved for patients who do not respond to moderate or high dose loop diuretics to minimize electrolyte abnormalities. (LoE: B) • In patients with HFrEF and NYHA class II to III symptoms, the use of an ARNI is recommended to reduce morbidity and mortality. (LoE: A) • In patients with previous or current symptoms of chronic HFrEF, the use of an ACE inhibitor is beneficial to reduce morbidity and mortality when the use of an ARNI is not feasible. (LoE: A) • In patients with previous or current symptoms of chronic HFrEF, who are intolerant to an ACE inhibitor because of cough or angioedema, and when the use of an ARNI is not feasible, the use of an ARB is recommended to reduce morbidity and mortality. (LoE: A) • In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality. (LoE: B) • ARNIs should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor. (LoE: B) • ARNI or ACE inhibitors should not be administered in patients with a history of angioedema. (LoE: C) • In patients with HFrEF, with current or previous symptoms, use of one of the three β-blockers proven to reduce mortality (e.g., bisoprolol, carvedilol, sustained-release metoprolol succinate) is recommended to reduce mortality and hospitalizations. (LoE: A) • In patients with HFrEF and NYHA class II to IV symptoms, a mineralocorticoid receptor antagonist (spironolactone or eplerenone) is recommended to reduce morbidity and mortality, if eGFR is >30 mL/min/1.73 m^2 and serum potassium is <5.0 mEq/L. Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely followed thereafter to minimize risk of hyperkalemia and renal insufficiency. (LoE: A) • In patients taking a mineralocorticoid receptor antagonist whose serum potassium cannot be maintained at <5.5 mEq/L, mineralocorticoid receptor

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	antagonist should be discontinued to avoid life threatening hyperkalemia. (LoE: B) • In patients with symptomatic chronic HFrEF, SGLT-2 an inhibitor is recommended to reduce hospitalization for HF and cardiovascular mortality, irrespective of the presence of type 2 diabetes. (LoE: A) • The combination of hydralazine and isosorbide dinitrate is recommended to improve symptoms and reduce morbidity and mortality for patients self-identified as African Americans with NYHA class III to IV HFrEF receiving optimal therapy. (LoE: A) • In patients with current or previous symptomatic HFrEF who cannot be given first-line agents, such as an ARNI, ACE inhibitor or ARB because of drug intolerance or renal insufficiency, a combination of hydralazine and isosorbide dinitrate might be considered to reduce morbidity and mortality. (LoE: C) • In patients with HF class II to IV symptoms, omega-3 polyunsaturated fatty acid supplementation may be reasonable to use as adjunctive therapy to reduce mortality and cardiovascular hospitalizations. (LoE: B) • In patients with chronic HFrEF without specific indication (e.g., venous thromboembolism, atrial fibrillation, a previous thromboembolic event, or a cardioembolic source, anticoagulation is not recommended. (LoE: B) • Dihydropyridine and non-dihydropyridine calcium channel blockers are not recommended for patients with HFrEF. (LoE: A) • In patients with HFrEF, vitamins, nutritional supplements, and hormonal therapy are not recommended other than to correct specific deficiencies. (LoE: B) • In patients with HFrEF, class IC antiarrhythmic medication and dronedarone may increase risk of mortality. (LoE: A) • In patients with HFrEF, thiazolidinediones increase the risk of worsening HF symptoms and hospitalizations. (LoE: A) • In patients with type 2 diabetes and high cardiovascular risk, the DPP-4 inhibitors, saxagliptin and alogliptin, increase the risk of HF hospitalization and should be avoided in patients with HF. (LoE: B) • In patients with HFrEF, nonsteroidal anti-inflammatory drugs worsen HF symptoms and should be avoided or withdrawn whenever possible. (LoE: B) • For patients with symptomatic (NYHA class II to III) stable chronic HFrEF (LVEF ≤35%) who are receiving guideline-directed medical therapy, including a maximally tolerated dose of a beta blocker, and who are in sinus rhythm with a heart rate of ≥70 beats per minute at rest, ivabradine can be beneficial to reduce HF hospitalizations and cardiovascular death. (LoE: B) • In patients with symptomatic HFrEF despite guideline-directed medical therapy or who are unable to tolerate guideline-directed medical therapy, digoxin might be considered to decrease hospitalizations for HF. (LoE: B) • In select high-risk patients with HFrEF and recent worsening of HF already on guideline-directed medical therapy, an oral soluble guanylate cyclase stimulator (vericiguat) may be considered to reduce HF hospitalization and cardiovascular death. (LoE: B) <u>Pharmacological treatment for Stage C HF with mildly reduced EF and improved EF</u> • In patients with HF with mildly reduced EF, SGLT-2 inhibitors can be beneficial in decreasing HF hospitalizations and cardiovascular mortality. (LoE: B) • Among patients with current or previous symptomatic HF with mildly reduced EF (LVEF, 41 to 49%), use of evidence-based beta blockers for HFrEF, ARNI, ACE inhibitor or ARB, and mineralocorticoid receptor antagonists may be considered to reduce the risk of HF hospitalization and cardiovascular mortality, particularly among patients with LVEF on the lower end of this spectrum. (LoE: B)

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	• In patients with HF with improved EF after treatment, guideline-directed medical therapy should be continued to prevent relapse of HF and LV dysfunction, even in patients who may become asymptomatic. (LoE: B) <u>Pharmacological treatment for Stage C HF with preserved EF (HFpEF)</u> • Patients with hypertension and HFpEF should have medication titrated to attain blood pressure targets in accordance with published clinical practice guidelines to prevent morbidity. (LoE: C) • SGLT-2 inhibitors can be beneficial in decreasing HF hospitalizations and cardiovascular mortality. (LoE: B) • In patients with HFpEF, the use of a mineralocorticoid receptor antagonist, ARB, or ARNI may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum. (LoE: B) • Routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or quality of life in patients with HFpEF is ineffective. (LoE: B) <u>Treatment of Stage D (advanced/refractory) HF</u> • For patients with advanced HF and hyponatremia, the benefit of fluid restriction to reduce congestive symptoms is uncertain. (LoE: C) • Continuous intravenous inotropic support is reasonable as "bridge therapy" in patients with HF (Stage D) refractory to guideline-directed medical therapy and device therapy who are eligible for and awaiting mechanical circulatory support or cardiac transplantation. (LoE: B) • In select patients with HF Stage D, despite optimal guideline-directed medical therapy and device therapy who are ineligible for either mechanical circulatory support or cardiac transplantation, continuous intravenous inotropic support may be considered as palliative therapy for symptom control and improvement in functional status. (LoE: B) • Long-term use of either continuous or intermittent, intravenous inotropic agents, for reasons other than palliative care or as a bridge to advanced therapies, is potentially harmful. (LoE: B)

American College of Cardiology Foundation/American Heart Association: **2014 American Heart Association/ American College of Cardiology Foundation Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes (2014)[15]**	<u>Early hospital care- standard medical therapies</u>
	• Supplemental oxygen should be administered to patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) with arterial oxygen saturation <90%, respiratory distress, or other high risk features of hypoxemia.
	• Anti-ischemic and analgesic medications
	  ○ Nitrates
	  ▪ Patients with NSTE-ACS with continuing ischemic pain should receive sublingual nitroglycerin (0.3 to 0.4 mg) every 5 minutes for up to three doses, after which an assessment should be made about the need for intravenous nitroglycerin.
	  ▪ Intravenous nitroglycerin is indicated for patients with NSTE-ACS for the treatment of persistent ischemia, heart failure, or hypertension.
	  ▪ Nitrates should not be administered to patients who recently received a phosphodiesterase inhibitor, especially within 24 hours of sildenafil or vardenafil, or within 48 hours of tadalafil.
	  ○ Analgesic therapy
	  ▪ In the absence of contraindications, it may be reasonable to administer morphine sulphate intravenously to patients with NSTE-ACE if there is continued ischemic chest pain despite treatment with maximally tolerated anti-ischemic medications.
	  ▪ Nonsteroidal anti-inflammatory drugs (NSAIDs) (except aspirin) should not be initiated and should be discontinued during hospitalization due to the increased risk of major adverse cardiac event associated with their use

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	○ Beta-adrenergic blockers ▪ Oral β-blocker therapy should be initiated within the first 24 hours in patients who do not have any of the following: 1) signs of HF, 2) evidence of low-output state, 3) increased risk for cardiogenic shock, or 4) other contraindications to β-blockade (e.g., PR interval >0.24 second, second- or third-degree heart block without a cardiac pacemaker, active asthma, or reactive airway disease) ▪ In patients with concomitant NSTE-ACS, stabilized heart failure, and reduced systolic function, it is recommended to continue β-blocker therapy with one of the three drugs proven to reduce mortality in patients with heart failure: sustained-release metoprolol succinate, carvedilol, or bisoprolol. ▪ Patients with documented contraindications to β-blockers in the first 24 hours should be re-evaluated to determine subsequent eligibility. ○ Calcium channel blockers (CCBs) ▪ In patients with NSTE-ACS, continuing or frequently recurring ischemia, and a contraindication to β-blockers, a nondihydropyridine CCB (e.g., verapamil or diltiazem) should be given as initial therapy in the absence of clinically significant LV dysfunction, increased risk for cardiogenic shock, PR interval >0.24 seconds, or second or third degree atrioventricular block without a cardiac pacemaker. ▪ Oral nondihydropyridine calcium antagonists are recommended in patients with NSTE-ACS who have recurrent ischemia in the absence of contraindications, after appropriate use of β-blockers and nitrates. ▪ CCBs are recommended for ischemic symptoms when β-blockers are not successful, are contraindicated, or cause unacceptable side effects. ▪ Long-acting CCBs and nitrates are recommended in patients with coronary artery spasm. ▪ Immediate-release nifedipine should not be administered to patients with NSTE-ACS in the absence of β-blocker therapy. ○ Other anti-ischemic interventions ▪ Ranolazine is currently indicated for treatment of chronic angina; however, it may also improve outcomes in NSTE-ACS patients due to a reduction in recurrent ischemia. ○ Cholesterol management ▪ High-intensity statin therapy should be initiated or continued in all patients with NSTE-ACS and no contraindications to its use. Treatment with statins reduces the rate of recurrent MI, coronary heart disease mortality, need for myocardial revascularization, and stroke. ▪ It is reasonable to obtain a fasting lipid profile in patients with NSTE-ACS, preferably within 24 hours of presentation. • Inhibitors of renin-angiotensin-aldosterone system ○ ACE inhibitors should be started and continued indefinitely in all patients with LVEF <0.40 and in those with hypertension, diabetes mellitus, or stable CKD, unless contraindicated. ○ ARBs are recommended in patients with heart failure or myocardial infarction with LVEF <0.40 who are ACE inhibitor intolerant. ○ Aldosterone-blockade is recommended in patients post-MI without significant renal dysfunction (creatinine >2.5 mg/dL in men or >2.0 mg/dL in women) or hyperkalemia (K >5.0 mEq/L) who are receiving therapeutic doses of ACE inhibitor and β-blocker and have a LVEF <0.40, diabetes mellitus, or heart failure. • Initial antiplatelet/anticoagulant therapy in patients with definite or likely NSTE-ACS treated with an initial invasive or ischemia-guided strategy ○ Non-enteric coated, chewable aspirin (162 to 325 mg) should be given to all patients with NSTE-ACS without contraindications as soon as possible

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	after presentation, and a maintenance dose of aspirin (81 to 162 mg/day) should be continued indefinitely. o In patients who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance, a loading dose of clopidogrel followed by a daily maintenance dose should be administered. o A $P2Y_{12}$ receptor inhibitor (clopidogrel or ticagrelor) in addition to aspirin should be administered for up to 12 months to all patients with NSTE-ACS without contraindications who are treated with an early invasive or ischemia-guided strategy. Options include: ▪ Clopidogrel: 300 or 600 mg loading dose, then 75 mg daily. ▪ Ticagrelor: 180 mg loading dose, then 90 mg twice daily. ▪ It is reasonable to use ticagrelor in preference to clopidogrel for $P2Y_{12}$ treatment in patients with NSTE-ACS who undergo an early invasive or ischemia-guided strategy. ▪ In patients with NSTE-ACS treated with an early invasive strategy and dual antiplatelet therapy (DAPT) with intermediate/high-risk features (e.g., positive troponin), a GP IIb/IIIa inhibitor may be considered as part of initial antiplatelet therapy. Preferred options are eptifibatide or tirofiban. ▪ Fibrinolytic therapy in patients with definite NSTE-ACS <u>Percutaneous coronary intervention (PCI)- Antiplatelet and anticoagulant therapy</u> • Antiplatelet agents o Patients already taking daily aspirin before PCI should take 81 to 325 mg non-enteric coated aspirin before PCI o Patients not on aspirin therapy should be given non-enteric coated aspirin 325 mg as soon as possible before PCI. o After PCI, aspirin should be continued indefinitely. o A loading dose of a $P2Y_{12}$ inhibitor should be given before the procedure in patients undergoing PCI with stenting. Options include clopidogrel 600 mg, prasugrel 60 mg, or ticagrelor 180 mg. o In patients with NSTE-ACS and high-risk features (e.g., elevated troponin) not adequately pretreated with clopidogrel or ticagrelor, it is useful to administer a GP IIb/IIIa inhibitor (abciximab, double-bolus eptifibatide, or high-dose bolus tirofiban) at the time of PCI. o In patients receiving a stent (bare metal or drug eluting) during PCI, $P2Y_{12}$ inhibitor therapy should be given for at least 12 months. Options include clopidogrel 75 mg daily, prasugrel 10 mg daily, or ticagrelor 90 mg twice daily. • Anticoagulant therapy o An anticoagulant should be administered to patients with NSTE-ACS undergoing PCI to reduce the risk of intracoronary and catheter thrombus formation. o Intravenous unfractionated heparin (UFH) is useful in patients with NSTE-ACS undergoing PCI. o Bivalirudin is useful as an anticoagulant with or without prior treatment with UFH. o An additional dose of 0.3 mg/kg intravenous enoxaparin should be administered at the time of PCI to patients with NSTE-ACS who have received fewer than two therapeutic subcutaneous doses or received the last subcutaneous enoxaparin dose eight to 12 hours before PCI. o If PCI is performed while the patient is on fondaparinux, an additional 85 IU/kg of UFH should be given intravenously immediately before PCI because of the risk of catheter thrombosis (60 IU/kg IV if a GP IIb/IIIa inhibitor used with UFH dosing based on the target-activated clotting time). o Anticoagulant therapy should be discontinued after PCI unless there is a

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	compelling reason to continue. • Timing of CABG in relation to use of antiplatelet agents o Non-enteric coated aspirin (81 to 325 mg daily) should be administered preoperatively to patients undergoing CABG. o In patients referred for elective CABG, clopidogrel and ticagrelor should be discontinued for at least five days before surgery and prasugrel for at least seven days before surgery. o In patients referred for urgent CABG, clopidogrel and ticagrelor should be discontinued for at least 24 hours to reduce major bleeding. o In patients referred for CABG, short-acting intravenous GP IIb/IIIa inhibitors (eptifibatide or tirofiban) should be discontinued for at least 2 to 4 hours before surgery and abciximab for at least 12 hours before to limit blood loss and transfusion. <u>Late hospital care, hospital discharge, and posthospital discharge care</u> • Medications at discharge o Medications required in the hospital to control ischemia should be continued after hospital discharge in patients with NSTE-ACS who do not undergo coronary revascularization, patients with incomplete or unsuccessful revascularization, and patients with recurrent symptoms after revascularization. Titration of the doses may be required. o All patients who are post–NSTE-ACS should be given sublingual or spray nitroglycerin with verbal and written instructions for its use. o Before hospital discharge, patients with NSTE-ACS should be informed about symptoms of worsening myocardial ischemia and MI and should be given verbal and written instructions about how and when to seek emergency care for such symptoms. o Before hospital discharge, patients who are post–NSTE-ACS and/or designated responsible caregivers should be provided with easily understood and culturally sensitive verbal and written instructions about medication type, purpose, dose, frequency, side effects, and duration of use. o For patients who are post–NSTE-ACS and have initial angina lasting more than one minute, nitroglycerin (one dose sublingual or spray) is recommended if angina does not subside within three to five minutes; call 9-1-1 immediately to access emergency medical services. o If the pattern or severity of angina changes, suggesting worsening myocardial ischemia (e.g., pain is more frequent or severe or is precipitated by less effort or occurs at rest), patients should contact their clinician without delay to assess the need for additional treatment or testing. o Before discharge, patients should be educated about modification of cardiovascular risk factors. • Late hospital and post-hospital oral antiplatelet therapy o Aspirin should be continued indefinitely. The dose should be 81 mg daily in patients treated with ticagrelor and 81 to 325 mg daily in all other patients. o In addition to aspirin, a $P2Y_{12}$ inhibitor (either clopidogrel or ticagrelor) should be continued for up to 12 months in all patients with NSTE-ACS without contraindications who are treated with an ischemia-guided strategy. o In patients receiving a stent (bare-metal stent or DES) during PCI for NSTE-ACS, P2Y12 inhibitor therapy should be given for at least 12 months. • Combined oral anticoagulant therapy and antiplatelet therapy in patients with NSTE-ACS o The duration of triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a $P2Y_{12}$ receptor inhibitor in patients with NSTE-ACS should be minimized to the extent possible to limit the risk of bleeding. o Proton pump inhibitors should be prescribed in patients with NSTE-ACS

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	with a history of gastrointestinal bleeding who require triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a $P2Y_{12}$ receptor inhibitor.
American Heart Association/American College of Cardiology/American College of Clinical Pharmacy/American Society for Preventive Cardiology/National Lipid Association/ Preventive Cardiovascular Nurses Association **Guideline for the Management of Patients With Chronic Coronary Disease (2023)**[16]	• In patients with chronic coronary disease (CCD), high-intensity statin therapy is recommended with the aim of achieving a ≥50% reduction in LDL-C levels to reduce the risk of major adverse cardiovascular events (MACE). • In patients in whom high-intensity statin therapy is contraindicated or not tolerated, moderate-intensity statin therapy is recommended with the aim of achieving a 30% to 49% reduction in LDL-C levels to reduce the risk of MACE. • In patients with CCD who are judged to be at very high risk and on maximally tolerated statin therapy with an LDL-C level ≥70 mg/dL, ezetimibe can be beneficial to further reduce the risk of MACE. • In patients with CCD who are judged to be at very high risk and who have an LDL-C level ≥70 mg/dL, or a non–high-density lipoprotein cholesterol (HDL-C) level ≥100 mg/dL, on maximally tolerated statin and ezetimibe, a PCSK9 monoclonal antibody can be beneficial to further reduce the risk of MACE. • In patients with CCD on maximally tolerated statin therapy with an LDL-C level <100 mg/dL and a persistent fasting triglyceride level of 150 to 499 mg/dL after addressing secondary causes, icosapent ethyl may be considered to further reduce the risk of MACE and cardiovascular death. • In patients with CCD who are not at very high risk and on maximally tolerated statin therapy with an LDL-C level ≥70 mg/dL, it may be reasonable to add ezetimibe to further reduce the risk of MACE. • In patients with CCD on maximally tolerated statin therapy who have an LDL-C level ≥70 mg/dL, and in whom ezetimibe and PCSK9 monoclonal antibody are deemed insufficient or not tolerated, it may be reasonable to add bempedoic acid or inclisiran (in place of PCSK9 monoclonal antibody) to further reduce LDL-C levels. • In patients with CCD receiving statin therapy, adding niacin, fenofibrate, or dietary supplements containing omega-3 fatty acids are not beneficial in reducing cardiovascular risk. • In adults with CCD, nonpharmacologic strategies are recommended as first-line therapy to lower BP in those with elevated BP (120-129/<80 mmHg). • In adults with CCD who have hypertension, a BP target of <130/<80 mmHg is recommended to reduce CVD events and all-cause death. • In adults with CCD and hypertension (systolic BP ≥130 and/or diastolic BP ≥80 mm Hg), in addition to nonpharmacological strategies, GDMT angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), or beta blockers are recommended as first-line therapy for compelling indications (e.g., recent MI or angina), with additional antihypertensive medications (e.g., dihydropyridine calcium channel blockers [CCB], long-acting thiazide diuretics, and/or mineralocorticoid receptor antagonists) added as needed to optimize BP control. • In patients with CCD and no indication for oral anticoagulant therapy, low-dose aspirin 81 mg (75 to 100 mg) is recommended to reduce atherosclerotic events. • In patients with CCD treated with PCI, dual antiplatelet therapy (DAPT) consisting of aspirin and clopidogrel for 6 months post PCI followed by single antiplatelet therapy (SAPT) is indicated to reduce MACE and bleeding events.* • In select patients with CCD treated with PCI and a drug-eluting stent (DES) who have completed a 1- to 3-month course of DAPT, P2Y12 inhibitor monotherapy for at least 12 months is reasonable to reduce bleeding risk. • In patients with CCD who have had a previous MI and are at low bleeding risk, extended DAPT beyond 12 months for a period of up to three years may be reasonable to reduce MACE. • In patients with CCD and a previous history of MI without a history of stroke,

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	transient ischemic attack (TIA), or ICH, vorapaxar may be added to aspirin therapy to reduce MACE. • In patients with CCD, the use of DAPT after CABG may be useful to reduce the incidence of saphenous vein graft occlusion. • In patients with CCD without recent ACS or a PCI-related indication for DAPT, the addition of clopidogrel to aspirin therapy is not useful to reduce MACE. • In patients with CCD and previous stroke, TIA, or ICH, vorapaxar should not be added to DAPT because of increased risk of major bleeding and ICH. • In patients with CCD and previous stroke, TIA, or ICH, prasugrel should not be used because of risk of significant or fatal bleeding. • In patients with CCD, chronic nonsteroidal anti-inflammatory drugs should not be used because of increased cardiovascular and bleeding complications. • In patients with CCD who have undergone elective PCI and who require oral anticoagulant therapy, DAPT for one to four weeks followed by clopidogrel alone for six months should be administered in addition to DOAC. • In patients with CCD who have undergone PCI and who require oral anticoagulant therapy, continuing aspirin in addition to clopidogrel for up to 1 month is reasonable if the patient has a high thrombotic risk and low bleeding risk. • In patients with CCD who require oral anticoagulation and have a low atherothrombotic risk, discontinuation of aspirin therapy with continuation of DOAC alone may be considered one year after PCI to reduce bleeding risk. • In patients with CCD who require oral anticoagulation, DOAC monotherapy may be considered if there is no acute indication for concomitant antiplatelet therapy. • In patients with CCD without an indication for therapeutic DOAC or DAPT and who are at high risk of recurrent ischemic events but low-to-moderate bleeding risk, the addition of low-dose rivaroxaban 2.5 mg twice daily to aspirin 81 mg daily is reasonable for long-term reduction of risk for MACE. • In patients with CCD on DAPT, the use of a PPI can be effective in reducing gastrointestinal bleeding risk. • In patients with CCD and LVEF ≤40% with or without previous MI, the use of beta-blocker therapy is recommended to reduce the risk of future MACE, including cardiovascular death. • In patients with CCD and LVEF<50%, the use of sustained release metoprolol succinate, carvedilol, or bisoprolol with titration to target doses is recommended in preference to other beta blockers. • In patients with CCD who were initiated on beta-blocker therapy for previous MI without a history of or current LVEF ≤50%, angina, arrhythmias, or uncontrolled hypertension, it may be reasonable to reassess the indication for long-term (>1 year) use of beta-blocker therapy for reducing MACE. • In patients with CCD without previous MI or LVEF ≤50%, the use of beta-blocker therapy is not beneficial in reducing MACE, in the absence of another primary indication for beta-blocker therapy. • In patients with CCD who also have hypertension, diabetes, LVEF ≤40%, or CKD, the use of ACE inhibitors, or ARBs if ACE inhibitor–intolerant, is recommended to reduce cardiovascular events. • In patients with CCD without hypertension, diabetes, or CKD and LVEF >40%, the use of ACE inhibitors or ARBs may be considered to reduce cardiovascular events. • In patients with CCD, the addition of colchicine for secondary prevention may be considered to reduce recurrent ASCVD events. • In patients with CCD, an annual influenza vaccination is recommended to reduce cardiovascular morbidity, cardiovascular death, and all-cause death. • In patients with CCD, coronavirus disease 2019 (COVID-19) vaccination is

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	recommended per public health guidelines to reduce COVID-19 complications. • In patients with CCD, a pneumococcal vaccine is reasonable to reduce cardiovascular morbidity and mortality and all-cause death. • In patients with CCD and angina, antianginal therapy with either a beta blocker, CCB, or long-acting nitrate is recommended for relief of angina or equivalent symptoms. • In patients with CCD and angina who remain symptomatic after initial treatment, addition of a second antianginal agent from a different therapeutic class (beta blockers, CCB, long-acting nitrates) is recommended for relief of angina or equivalent symptoms. • In patients with CCD, ranolazine is recommended in patients who remain symptomatic despite treatment with beta blockers, CCB, or long-acting nitrate therapies. • In patients with CCD, sublingual nitroglycerin or nitroglycerin spray is recommended for immediate short-term relief of angina or equivalent symptoms. • In patients with CCD and normal LV function, the addition of ivabradine to standard anti-anginal therapy is potentially harmful. • In patients with CCD and lifestyle-limiting angina despite GDMT and with significant coronary artery stenoses amenable to revascularization, revascularization is recommended to improve symptoms. • In patients with CCD who have experienced SCAD, beta-blocker therapy may be reasonable to reduce the incidence of recurrent SCAD. • Women with CCD who are contemplating pregnancy or who are pregnant should not use ACE inhibitors, ARBs, direct renin inhibitors, angiotensin receptor-neprilysin inhibitors, or aldosterone antagonists during pregnancy to prevent harm to the fetus. • Women with CCD should not receive systemic postmenopausal hormone therapy because of a lack of benefit on MACE and mortality, and an increased risk of venous thromboembolism.

European Society of Cardiology: **Guidelines for the Diagnosis and Management of Chronic Coronary Syndromes (2019)**[17]	<u>Pharmacological management of stable coronary artery disease (CAD) patients</u>
	• The two aims of the pharmacological management of stable CAD patients are to obtain relief of symptoms and to prevent CV events.
	• Optimal medical treatment indicates at least one drug for angina/ischaemia relief plus drugs for event prevention.
	• It is recommended to educate patients about the disease, risk factors and treatment strategy.
	• It is indicated to review the patient's response soon after starting therapy.
	• Concomitant use of a proton pump inhibitor is recommended in patients receiving aspirin monotherapy, DAPT, or DOAC monotherapy who are at high risk of gastrointestinal bleeding.
	• Lipid-lowering drugs: if goals are not met on maximum tolerated dose of a statin, consideration of combination therapy with ezetimibe or a PCSK9 inhibitor is recommended
	• ACE inhibitors should be considered in patients at a very high risk of cardiovascular adverse events
	• Angina/ischemia relief:
	  ○ Short-acting nitrates are recommended.
	  ○ First-line treatment is indicated with ß-blockers and/or calcium channel blockers to control heart rate and symptoms.
	  ○ Long-acting nitrates should be considered as a second-line treatment option when initial therapy with a beta-blocker and/or a non-DHP-calcium channel blocker is contraindicated, poorly tolerated, or inadequate in controlling angina symptoms
	  ○ Nicorandil, ranolazine, ivabradine, or trimetazidine should be

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	considered as a second-line treatment to reduce angina frequency and improve exercise tolerance in subjects who cannot tolerate, have contraindications to, or whose symptoms are not adequately controlled by beta-blockers, CCBs, and long-acting nitrates. o According to comorbidities/tolerance, it is indicated to use second-line therapies as first-line treatment in selected patients. o In asymptomatic patients with large areas of ischaemia (>10%) ß-blockers should be considered. o In patients with vasospastic angina, calcium channel blockers and nitrates should be considered and beta-blockers avoided. • Event prevention: o Low-dose aspirin daily is recommended in all stable CAD patients. o Clopidogrel is indicated as an alternative in case of aspirin intolerance. o Statins are recommended in all stable CAD patients. o It is recommended to use ACE inhibitors (or ARBs) if presence of other conditions (e.g., heart failure, hypertension or diabetes). <u>Treatment in patients with microvascular angina</u> • It is recommended that all patients receive secondary prevention medications including aspirin and statins. • ß-blockers are recommended as a first-line treatment. • Calcium antagonists are recommended if ß-blockers do not achieve sufficient symptomatic benefit or are not tolerated. • ACE inhibitors or nicorandil may be considered in patients with refractory symptoms. • Xanthine derivatives or nonpharmacological treatments such as neurostimulatory techniques may be considered in patients with symptoms refractory to the above listed drugs. <u>Stenting and peri-procedural antiplatelet strategies in stable CAD patients</u> • Drug-eluting stent (DES) is recommended in stable CAD patients undergoing stenting if there is no contraindication to prolonged dual antiplatelet therapy (DAPT). • Aspirin is recommended for elective stenting. • Clopidogrel is recommended for elective stenting. • Prasugrel or ticagrelor should be considered in patients with stent thrombosis on clopidogrel without treatment interruption. • GP IIb/IIIa antagonists should be considered for bailout situation only. • Platelet function testing or genetic testing may be considered in specific or high-risk situations (e.g., prior history of stent thrombosis; compliance issue; suspicion of resistance; high bleeding risk) if results may change the treatment strategy. • Prasugrel or ticagrelor may be considered in specific high-risk situations of elective stenting (e.g., left main stenting, high risk of stent thrombosis, diabetes). • Pretreatment with clopidogrel (when coronary anatomy is not known) is not recommended. • Routine platelet function testing (clopidogrel and aspirin) to adjust antiplatelet therapy before or after elective stenting is not recommended. • Prasugrel or ticagrelor is not recommended in low-risk elective stenting. • After uncomplicated PCI, early cessation (≤1 week) of aspirin, and continuation of dual therapy with oral anticoagulation therapy and clopidogrel should be considered if the risk of stent thrombosis is low. • Triple therapy with aspirin, clopidogrel, and a DOAC for ≥1 month should be considered when the risk of stent thrombosis outweighs the bleeding risk, with a

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	total of no more than six months. <u>Follow-up of revascularized stable coronary artery disease patients</u> • It is recommended that all revascularized patients receive a secondary prevention and be scheduled for follow-up visit. • It is recommended to instruct patients before discharge about return to work and reuptake of full activities. Patients have to be advised to seek immediate medical contact if symptoms (re-) occur. • Single antiplatelet therapy, usually aspirin, is recommended indefinitely. • DAPT is indicated after bare metal stent (BMS) for at least one month. • DAPT is indicated for six to 12 months after second generation DES. • DAPT may be used for more than one year in patients at high ischemic risk (e.g., stent thrombosis, recurrent acute coronary syndrome on DAPT, post MI/diffuse CAD) and low bleeding risk. • DAPT for one to three months may be used after DES implantation in patients at high bleeding risk or with undeferrable surgery or concomitant anticoagulant treatment. <u>Antithrombotic therapy in patients with chronic coronary syndrome:</u> • Addition of a second antithrombotic drug to aspirin for long-term secondary prevention should be considered in patients with at least a moderately increased risk of ischemic events and without high bleeding risk. • When oral anticoagulation is initiated in patients with AF, a DOAC is recommended in preference to VKA therapy.
European Society of Cardiology: **Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (2021)[18]**	<u>Pharmacological treatments indicated in patients with (NYHA Class II-IV) heart failure with reduced ejection fraction</u> • An ACE inhibitor is recommended, in addition to a β-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death. • A mineralocorticoid receptor antagonist (MRA) is recommended for patients with HFrEF, who remain symptomatic despite treatment with an ACE inhibitor and a β-blocker, to reduce the risk of HF hospitalization and death. • Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death. Dapagliflozin or empagliflozin are recommended, in addition to optimal medical therapy with an ACE-I/ARNI, a β-blocker and an MRA, for patients with HFrEF regardless of diabetes status. • Sacubitril-valsartan is recommended as a replacement for an ACE inhibitor to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE inhibitor, a β-blocker, and a mineralocorticoid receptor antagonist. • Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion. • Ivabradine should be considered to reduce the risk of HF hospitalization or cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm despite treatment with an evidence-based dose of β-blocker (or maximum tolerated dose below that), ACE inhibitor (or ARB), and a mineralocorticoid receptor antagonist (or ARB). • Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm who are unable to tolerate or have contraindications for a β-blocker. Patients should also receive an ACE inhibitor (or ARB) and a mineralocorticoid receptor antagonist (or ARB). • An ARB is recommended to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients unable to tolerate an ACE inhibitor (patients should also receive a β-blocker and mineralocorticoid receptor antagonist).

Clinical Guideline	Recommendations
	• An ARB may be considered to reduce the risk of HF hospitalization and death in patients who are symptomatic despite treatment with a β-blocker who are unable to tolerate a mineralocorticoid receptor antagonist. • Vericiguat may be considered in patients in NYHA class II-IV who have had worsening HF despite treatment with an ACE-I (or ARNI), a β-blocker and an MRA to reduce the risk of CV mortality or HF hospitalization. • Hydralazine and isosorbide dinitrate should be considered in self-identified black patients with LVEF ≤35% or with an LVEF <45% combined with a dilated LV in NYHA Class III–IV despite treatment with an ACE-I a β-blocker and a mineralocorticoid receptor antagonist to reduce the risk of HF hospitalization and death. • Hydralazine and isosorbide dinitrate may be considered in symptomatic patients with HFrEF who can tolerate neither an ACE inhibitor nor an ARB (or they are contraindicated) to reduce the risk of death. • Digoxin is a treatment with less-certain benefits and may be considered in symptomatic patients in sinus rhythm despite treatment with an ACE inhibitor (or ARB), a β-blocker and a mineralocorticoid receptor antagonist, to reduce the risk of hospitalization (both all-cause and HF-hospitalizations). <u>Recommendations for treatment of patients with (NYHA class II-IV) heart failure with mildly reduced ejection fraction (HFmrEF)</u> • Diuretics are recommended in patients with congestion and HFmrEF in order to alleviate symptoms and signs. • An ACE inhibitor may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • An ARB may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • A β-blocker may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • An MRA may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • Sacubitril/valsartan may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. <u>Recommendations for treatment of patients with heart failure with preserved ejection fraction (HFpEF)</u> • It is recommended to screen patients with HFpEF for both cardiovascular and noncardiovascular comorbidities, which, if present, should be treated provided safe and effective interventions exist to improve symptoms, well-being and/or prognosis. • Diuretics are recommended in congested patients with HFpEF in order to alleviate symptoms and signs. <u>Recommendations for the primary prevention of heart failure in patients with risk factors for its development</u> • Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life. • Treatment with statins is recommended in patients at high risk of CV disease or with CV disease in order to prevent or delay the onset of HF, and to prevent HF hospitalizations. • SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with diabetes at high risk of CV disease or with CV disease in order to prevent HF hospitalizations. • Counselling against sedentary habit, obesity, cigarette smoking, and alcohol abuse is recommended to prevent or delay the onset of HF.

Clinical Guideline	Recommendations
	<u>Recommendations for the initial management of patients with acute heart failure – pharmacotherapy</u> • Intravenous loop diuretics are recommended for all patients with acute HF admitted with signs/symptoms of fluid overload to improve symptoms. It is recommended to regularly monitor symptoms, urine output, renal function and electrolytes during use of intravenous diuretics. • Combination of a loop diuretic with thiazide type diuretic should be considered in patients with resistant oedema who do not respond to an increase in loop diuretic doses. • In patients with acute HF and SBP >110 mmHg, intravenous vasodilators may be considered as initial therapy to improve symptoms and reduce congestion. • Inotropic agents may be considered in patients with SBP <90 mmHg and evidence of hypoperfusion who do not respond to standard treatment, including fluid challenge, to improve peripheral perfusion and maintain end-organ function. • Inotropic agents are not recommended routinely, due to safety concerns, unless the patient has symptomatic hypotension and evidence of hypoperfusion. • A vasopressor, preferably norepinephrine, may be considered in patients with cardiogenic shock to increase blood pressure and vital organ perfusion. • Thromboembolism prophylaxis (e.g., with LMWH) is recommended in patients not already anticoagulated and with no contraindication to anticoagulation, to reduce the risk of deep venous thrombosis and pulmonary embolism. • Routine use of opiates is not recommended, unless in selected patients with severe/intractable pain or anxiety.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the direct vasodilators are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Direct Vasodilators[1-4]

Indication	Single Entity Agents		Combination Products
	Hydralazine	Minoxidil	Isosorbide Dinitrate and Hydralazine
Heart Failure			
Treatment of heart failure as an adjunct to standard therapy in self-identified black patients to improve survival, to prolong time to hospitalization for heart failure, and to improve patient-reported functional status			✔
Hypertension			
Treatment of essential hypertension	✔ *		
Treatment of hypertension		✔ †	
Treatment of severe essential hypertension	✔ ‡		

*Tablet: Alone or as an adjunct.
†Because of the potential for serious adverse effects, minoxidil tablet is only indicated for the treatment of hypertension that is symptomatic or associated with target organ damage and is not manageable with maximum therapeutic doses of a diuretic plus two other antihypertensive drugs. At the present time use in milder degrees of hypertension is not recommended because the benefit-risk relationship has not been defined.
‡Injection: When the drug cannot be given orally or when there is an urgent need to lower blood pressure.

IV. Pharmacokinetics

The pharmacokinetic parameters of the direct vasodilators are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Direct Vasodilators[2]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Hydralazine	38 to 50	88 to 90	Liver, significant (% not reported)	Renal (3 to 14) Feces (3 to 12)	3 to 5
Minoxidil	90 to 100	Insignificant (% not reported)	Liver (90)	Renal (90) Feces (3)	4.2
Combination Products					
Isosorbide dinitrate and hydralazine	H: 10 to 26 I: ~25	H: 88 to 90 I: 28	H: Liver, significant (% not reported) I: Liver, significant (% not reported)	H: Not reported I: Not reported	H: 3 to 5 I: 2

H=hydralazine, I=isosorbide dinitrate

V. Drug Interactions

Significant drug interactions with the direct vasodilators are listed in Table 5.

Table 5. Significant Drug Interactions with the Direct Vasodilators[2]

Generic Name(s)	Interaction	Mechanism
Nitrates and nitrites	Phosphodiesterase type 5 inhibitors	Sildenafil may potentiate the hypotensive effects of nitrates. The use of these agents in combination is contraindicated.
Nitrates and nitrites	Avanafil	Concurrent use of avanafil and isosorbide dinitrate may result in potentiation of hypotensive effects.
Nitrates and nitrites	Riociguat	Concurrent use of riociguat and nitrates may result in increased risk of hypotension.

VI. Adverse Drug Events

The most common adverse drug events reported with the direct vasodilators are listed in Table 6. The boxed warning for minoxidil is listed in Table 7.

Table 6. Adverse Drug Events (%) Reported with the Direct Vasodilators[1-4]

Adverse Events	Single Entity Agents		Combination Products
	Hydralazine	Minoxidil	Isosorbide Dinitrate and Hydralazine
Cardiovascular System			
Angina pectoris	✔	✔	16
Cardiovascular collapse	-	-	✔
Crescendo angina	-	-	✔
Electrocardiogram changes	-	60	-
Flushing	✔	-	✔
Heart failure	-	✔	-
Hypotension	-	-	8
Orthostatic hypotension	✔	-	✔
Pallor	-	-	✔

Adverse Events	Single Entity Agents		Combination Products
	Hydralazine	Minoxidil	Isosorbide Dinitrate and Hydralazine
Palpitations	✔	-	4
Paradoxical pressor response	✔	-	✔
Peripheral edema	✔	7	✔
Pericardial effusion with tamponade	-	3	-
Pericarditis	-	✔	-
Postural hypotension	-	✔	✔
Rebound hypertension	-	-	✔
Shock	-	-	✔
Syncope	-	-	✔
Tachycardia	✔	✔	2
Vascular collapse	✔	-	✔
Ventricular tachycardia	-	-	4
Central Nervous System			
Anxiety	✔	-	✔
Asthenia	✔	-	✔
Chills	✔	-	✔
Depression	✔	-	✔
Disorientation	✔	-	✔
Dizziness	✔	-	32
Fever	✔	-	✔
Headache	✔	-	50
Lightheadedness	-	-	✔
Psychotic reaction	✔	-	✔
Restlessness	-	-	✔
Dermatological			
Alopecia	-	-	1
Hypertrichosis	-	80	-
Pruritus	✔	-	✔
Rash	✔	✔	✔
Stevens-Johnson syndrome	-	✔	-
Urticaria	✔	-	✔
Endocrine and Metabolic			
Breast tenderness	-	✔	-
Fluid and electrolyte imbalance	-	✔	-
Hyperglycemia	-	-	4
Hyperlipidemia	-	-	3
Gastrointestinal			
Anorexia	✔	-	✔
Bowel incontinence	-	-	✔
Constipation	✔	-	✔
Diarrhea	✔	-	✔
Nausea	✔	✔	10
Paralytic ileus	✔	-	✔
Vomiting	✔	✔	4
Weight gain	-	✔	-
Xerostomia	-	-	✔
Genitourinary			
Blood urea nitrogen increased	-	✔	-
Dysuria	✔	-	✔
Impotence	✔	-	✔
Serum creatine increased	-	✔	-
Urinary incontinence	-	-	✔

Adverse Events	Single Entity Agents		Combination Products
	Hydralazine	Minoxidil	Isosorbide Dinitrate and Hydralazine
Hematological			
Agranulocytosis	✔	-	✔
Eosinophilia	✔	-	✔
Erythrocyte count reduced	✔	✔	✔
Hematocrit decreased	-	✔	-
Hemoglobin decreased	✔	✔	✔
Hemolytic anemia	✔	-	✔
Leukopenia	✔	✔	✔
Methemoglobinemia	-	-	✔
Thrombocytopenia	✔	✔	✔
Hepatic			
Alkaline phosphatase increased	-	✔	-
Cholecystitis	-	-	1
Musculoskeletal			
Arthralgia	-	-	1
Muscle cramps	✔	-	✔
Myalgia	-	-	1
Paresthesia	-	-	4
Peripheral neuritis	✔	-	✔
Rheumatoid arthritis	✔	-	✔
Tendon disorder	-	-	1
Tremor	✔	-	✔
Weakness	✔	-	14
Ocular			
Blurred vision	-	-	✔
Conjunctivitis	✔	-	✔
Lacrimation	✔	-	✔
Respiratory			
Bronchitis	-	-	8
Dyspnea	✔	-	✔
Nasal congestion	✔	-	✔
Pulmonary edema	-	✔	-
Rhinitis	-	-	4
Sinusitis	-	-	4
Other			
Allergic reactions	-	-	1
Angioedema	-	-	1
Diaphoresis	✔	-	1
Drug-induced lupus-like syndrome	✔	-	✔

✔ Percent not specified
- Event not reported

Table 7. Boxed Warning for Minoxidil[1]

WARNING
Minoxidil may produce serious adverse effects. It can cause pericardial effusion, occasionally progressing to tamponade, and it can exacerbate angina pectoris. Reserve for hypertensive patients who do not respond adequately to maximum therapeutic doses of a diuretic and two other antihypertensive agents. In experimental animals, minoxidil caused several kinds of myocardial lesions and other adverse cardiac effects.

Administer under close supervision, usually concomitantly with a β-adrenergic blocking agent, to prevent tachycardia and increased myocardial workload. Usually, it must be given with a diuretic, frequently one acting in the ascending limb of the loop of Henle to prevent serious fluid accumulation. When first administering minoxidil, hospitalize and monitor patients with malignant hypertension and those already receiving guanethidine to avoid too rapid or large orthostatic decreases in blood pressure.

VII. Dosing and Administration

The usual dosing regimens for the direct vasodilators are listed in Table 8.

Table 8. Usual Dosing Regimens for the Direct Vasodilators[1-4]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Hydralazine	Essential hypertension: Injection, tablet: initial, 10 mg four times daily for the first two to four days, followed by 25 mg four times daily for the balance of the first week, then for the second and subsequent weeks, increase dosage to 50 mg four times daily; maintenance, adjust dosage to the lowest effective levels	Essential hypertension: Safety and effectiveness in pediatric patients have not been established in controlled clinical trials, although there is experience with the use of hydralazine in pediatric patients. Injection, tablet: initial, 0.75 mg/kg/day administered in four divided doses; maintenance, dosage may be increased gradually over the next three to four weeks; maximum, 7.5 mg/kg or 200 mg/day	Injection: 20 mg/mL Tablet: 10 mg 25 mg 50 mg 100 mg
Minoxidil	Hypertension: Tablet: initial, 5 mg/day and increase gradually every three days; maintenance, 10 to 40 mg daily in single or divided doses; maximum, 100 mg/day	Hypertension: Tablet: initial, 0.2 mg/kg/day; maintenance, 0.25 to 1 mg/kg/day; maximum, 50 mg/day	Tablet: 2.5 mg 10 mg
Combination Products			
Isosorbide dinitrate and hydralazine	Heart failure: Tablet: initial, 20-37.5 mg three times daily; maximum, 40-75 mg (two tablets) three times daily	The safety and effectiveness have not been established in children.	Tablet: 20-37.5 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the direct vasodilators are summarized in Table 9.

Table 9. Comparative Clinical Trials with the Direct Vasodilators

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Heart Failure				
Unverferth et al.[19] (1983) Hydralazine 225 mg/day vs ISDN 160 mg/day vs hydralazine and ISDN (individual agents) vs placebo	DB, PC, RCT Patients with idiopathic dilated cardiomyopathy were evaluated to determine the hemodynamic and morphologic effects of vasodilator therapy	N=49 3 months	Primary: Echocardiographic percent change of left ventricular diameter, the systolic time intervals ratio of PEP/LVET, the pulmonary capillary wedge pressure, mean pulmonary artery pressure, pulmonary vascular resistance, cardiac index, and SVR Secondary: Not reported	Primary: For the percent change in left ventricular diameter and PEP/LVET, a significant improvement with hydralazine and combination therapy ($P<0.05$) was seen compared to ISDN alone or placebo. Significant decrease with ISDN and combination therapy vs placebo or hydralazine alone ($P<0.05$) was seen for pulmonary capillary wedge pressure, mean pulmonary artery pressure, and the pulmonary vascular resistance. Hydralazine resulted in a decrease in SVR and increase in cardiac index from 2.5±0.4 to 3.1±0.4 L/min/m^2 vs placebo or ISDN alone ($P<0.05$). Combination therapy resulted in a decrease in SVR and cardiac index increased from 2.3±0.4 to 3.1±0.4 L/min/m^2 ($P<0.01$). There was no improvement in SVR or cardiac index with ISDN alone or with placebo. Myocardial cell diameter decreased from 25.4±3.1 microns at baseline to 23.1±3.8 microns with hydralazine ($P<0.05$). Combination therapy decreased its cell diameter from 23.9±3.7 to 22.2±2.2 microns ($P<0.05$). There was no change in the myocardial cell diameter seen in patients treated with ISDN alone or with placebo. Secondary: Not reported
Taylor[20] (2005) A-HeFT	DB, MC, PC, RCT African American	N=1,050 6 to 18 months	Primary: Composite score (all-cause	Primary: Mortality in the fixed-dose ISDN and hydralazine group was 6.2% compared to 10.2% in the placebo group ($P=0.02$).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ISDN and hydralazine 60-112.5 mg/day in 3 divided doses, titrated up to ISDN and hydralazine 120-225 mg/day in 3 divided doses (fixed-dose combination product) vs placebo	patients with moderate-to-severe symptomatic heart failure, classified NYHA class III to IV heart failure with dilated ventricles and low ejection fractions		mortality, first hospitalization for heart failure, and quality of life at 6 months as measured by the Minnesota Living with Heart Failure questionnaire) Secondary: Not reported	Survival was increased by 43% in the active treatment arm (HR, 0.57; P=0.02). The composite score and all individual components of the composite score were significantly and positively impacted by treatment with ISDN and hydralazine (primary composite score P=0.01, death from any cause P=0.02, first hospitalization for heart failure P=0.001, change in quality of life score at 6 months P=0.02). The study was prematurely terminated in as a result of the significantly improved survival in the ISDN and hydralazine group. Secondary: Not reported
Taylor et al.[21] (2004) A-HeFT ISDN and hydralazine 20-37.5 mg TID, increased to ISDN and hydralazine 40-75 mg TID (fixed-dose combination product) vs placebo	DB, MC, PC, RCT Patients ≥18 years of age, self-identified as of African descent, with NYHA class III or IV heart failure on standard therapy for ≥3 months and evidence of left ventricular dysfunction within the prior 6 months	N=1,050 18 months (mean duration of follow-up was 10 months)	Primary: A composite score made up of weighted values for death from any cause, a first hospitalization for heart failure, and quality of life changes Secondary: Individual components of the primary composite score	Primary: From a range of possible scores of -6 to 2 for the composite endpoint, patients in the active treatment group achieved a significantly better score of -0.1±1.9 compared -0.5±2.0 in the placebo group (P=0.01). Secondary: There was a significantly higher mortality rate in the placebo group compared to the ISDN and hydralazine group (6.2 vs 10.2%; P=0.02). Survival was increased by 43% in the active treatment group (HR, 0.57; P=0.02). This led to the early termination of the trial. Compared to the placebo group, the rate of first hospitalization for heart failure was significantly reduced in the ISDN and hydralazine group (16.4 vs 24.4%; P=0.001). There was a significant improvement in quality of life scores found with the ISDN and hydralazine group when compared to the placebo group (-5.6±20.6 vs -2.7±21.2; P=0.02).
Taylor et al.[22] (2007) A-HeFT	Post-hoc analysis of A-HeFT	N=1,050 Mean duration	Primary: Cause specific mortality, event	Primary: Cardiovascular deaths were significantly reduced in the treatment group compared to the placebo group (5.0 vs 8.5%; P=0.027). Pump failure

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ISDN and hydralazine 20-37.5 mg TID, increased to ISDN and hydralazine 40-75 mg TID (fixed-dose combination product) vs placebo	Patients ≥18 years of age, self-identified as of African descent, with NYHA class III or IV heart failure on standard therapy for ≥3 months and evidence of left ventricular dysfunction within the prior 6 months	of follow-up was 18 months	free survival (time to either death or first hospitalization and time to first hospitalization for heart failure Secondary: Subgroup analysis	death was also significantly reduced (75%) compared to the placebo group (0.8 vs 3.0%; P=0.012). There were no significant differences between the groups for other causes of death. In the treatment group event-free survival (death or first hospitalization for heart failure) was significantly improved compared to the placebo group (HR, 0.63; 95% CI, 0.49 to 0.81; P<0.001). The time to first hospitalization for heart failure was also significantly reduced (HR, 0.61; 95% CI, 0.46 to 0.80; P<0.001). Secondary: A consistent beneficial effect was seen in the treatment sub groups (age, sex, baseline BP, history of chronic renal insufficiency, presence of diabetes, cause of heart failure, and baseline medication use) on primary composite score and event-free survival.
Anand et al.[23] (2014) A-HeFT ISDN and hydralazine 20-37.5 mg TID, increased to ISDN and hydralazine 40-75 mg TID (fixed-dose combination product) vs placebo	Post-hoc analysis of A-HeFT Patients ≥18 years of age, self-identified as of African descent, with NYHA class III or IV heart failure on standard therapy for ≥3 months and evidence of left ventricular dysfunction within the prior 6 months	N=1,050 Mean duration of follow-up was 18 months	Primary: Mortality, all hospitalizations including recurrences (first hospitalizations only, all hospitalizations including recurrences, 30-day all-cause readmission rates) Secondary: Not reported	Primary: During a median follow-up of 450 days, 86 (8.2%) patients died. The cumulative mortality was significantly lower (HR, 0.57; 95% CI, 0.37 to 0.89; P=0.013) in the treatment group vs the placebo group. When deaths were analyzed as a competing risk for first hospitalizations, the effect (HR) of treatment was 0.88 (95% CI, 0.72 to 1.06; P=0.18) on hospitalization for any cause and 0.61 (95% CI, 0.47 to 0.80; P<0.001) on heart failure hospitalizations. The use of fixed-dose combination product was associated with a significant 25% reduction in all hospitalizations for any cause (HR, 0.75; 95% CI, 0.63 to 0.91; P=0.003) and a 34% reduction in all heart failure hospitalizations (HR, 0.66; 95% CI, 0.52 to 0.83; P<0.001). Of the subjects who had at least one admission for heart failure and were discharged alive, 29 of 123 (23.6%) in the placebo group and 12 of 81 (14.8%) in the combination product group were readmitted for any cause <30 days of being discharged from their first hospitalization for heart failure. This reduction in the 30-day all-cause readmissions by the combination product was not statistically significant.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Yancy et al.[24] (2007) A-HeFT ISDN and hydralazine 20-37.5 mg TID, increased to ISDN and hydralazine 40-75 mg TID (fixed-dose combination product) vs placebo	ES, OL Patients previously enrolled in A-HeFT with NYHA class I to IV heart failure symptoms while receiving background therapy and satisfying the A-HeFT inclusion criteria	N=158 12 months or until ISDN and hydralazine approved by the FDA	Primary: Compliance with study drug, safety, tolerability Secondary: Change in NYHA association class, death, hospitalization for heart failure	Primary: Compliance in the treatment group averaged 87±25%, with no significant difference when compared to the placebo group. There were no significant differences in adverse events between the groups. Secondary: No significant difference was seen in hospitalizations from heart failure according to randomization. The greatest improvement in heart failure symptoms occurred in NYHA class III (at baseline) compared to other classes (P<0.001). Overall most patients were unchanged with 24% showing improved NYHA class and 9% showing a worsening.
Cohn et al.[25] (1986) V-HeFT I Hydralazine 300 mg/day plus ISDN 160 mg/day (individual agents, concurrent therapy) vs prazosin 20 mg/day vs	AC, DB, PC, RCT Men with impaired cardiac function and reduced exercise tolerance on digoxin and a diuretic	N=642 3 years	Primary: Mortality Secondary: Effect on left ventricular function	Primary: There was a 34% risk reduction in mortality by two years in the hydralazine plus ISDN group compared to placebo (P<0.028). Cumulative mortality rates of 25.6 and 36.2% were observed in the hydralazine plus ISDN group at 2 and 3 years respectively, compared to 34.3 and 46.9% in the placebo group. The results found in the prazosin group were similar to placebo. Secondary: A significant increase in the left ventricular ejection fraction was reported at eight weeks and one year in the hydralazine plus ISDN treatment group, but not in either the prazosin or placebo groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				
Cohn et al.[26] (1991) V-HeFT II Hydralazine 300 mg/day plus ISDN 160 mg/day vs enalapril 20 mg/day	AC, DB, MC, RCT Men between the ages of 18 and 75 years with chronic heart failure receiving digoxin and diuretic therapy	N=804 2 years	Primary: Mortality Secondary: Peak oxygen consumption during exercise, LVEF	Primary: Mortality after two years was significantly lower in the group treated with enalapril (18%) than hydralazine plus isosorbide dinitrate (25%; P=0.016), and overall mortality tended to be lower (P=0.08). The lower mortality in the enalapril arm was attributable to a reduction in the incidence of sudden death, and this beneficial effect was more prominent in patients with less severe symptoms (NYHA class I or II). Secondary: Peak oxygen consumption during exercise was increased only by hydralazine plus isosorbide dinitrate (P<0.05). While LVEF increased with both regimens during the two years after randomization, LVEF increased more (P<0.05) during the first 13 weeks in the hydralazine plus isosorbide dinitrate group.
Mullens et al.[27] (2009) Isosorbide dinitrate and hydralazine (I/H) added to an ACE inhibitor or angiotensin receptor blockers vs ACE inhibitor or angiotensin receptor blockers Titration of oral drugs was aimed to wean off parental	PRO Patients ≥18 years of age with advanced decompensate heart failure with a cardiac index <2.2 L/min/m^2 who were admitted to the hospital for intensive medical therapy	N=239 Mean 26.3 months	Primary: All-cause mortality, cardiac transplantation, and first readmission for heart failure after index hospitalization discharge Secondary: Not reported	Primary: Patients receiving I/H had lower all-cause mortality (34 vs 41%; OR, 0.65; 95% CI, 0.43 to 0.99, P=0.04) and lower all-cause mortality/heart failure rehospitalization (70% vs 85%; OR, 0.72; 95% CI, 0.54 to 0.97; P=0.03) compared to the control group. There was no difference in overall cardiac transplantation or heart failure rehospitalization rates among the treatment groups. The improved outcomes in the I/H group was independent of race; however, there was a trend toward improved outcomes in African-Americans (all-cause mortality for whites in the I/H group, OR 0.66; 95% CI, 0.4 to 0.98; P=0.05; all-cause mortality for African-Americans in the I/H group, OR 0.44; 95% CI, 0.23 to 0.85; P=0.01). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
therapy and based on maintaining a target mean arterial pressure of 65 to 70 mm Hg and/or systolic blood pressure >85 mm Hg				
Hypertension				
Johnson et al.[28] (1983) Minoxidil 5 to 40 mg/day as add-on therapy vs hydralazine 25 to 200 mg/day as add-on therapy	DB, RCT Patients with normal renal function receiving HCTZ or propranolol (doses unknown) with DBP >95 mmHg	N=36 28 weeks	Primary: Percentage of patients with DBP <90 mmHg at weeks 4 and 28 Secondary: Not reported	Primary: There were greater response rates (DBP <90 mmHg) with minoxidil (69%) vs hydralazine (35%) at week four. At week 28, there were greater response rates (DBP <90 mmHg) with minoxidil (55%) vs hydralazine (40%). Secondary: Not reported
Bevan et al.[29] (1993) Captopril (unknown dose) vs hydralazine (unknown dose) vs nifedipine (unknown dose)	DB, PC, RCT Patients with inadequately controlled HTN, despite treatment with atenolol 100 mg/day and bendrofluazide* 5 mg/day	N=160 12 weeks	Primary: Comparative antihypertensive, biochemical, adverse effects Secondary: Not reported	Primary: Mean supine blood pressure changes: captopril 13.4/10.3 mmHg, hydralazine 15.0/10.0 mmHg, and nifedipine 16.8/8.1 mmHg (differences not significant). Erect blood pressure changes were similar; target blood pressure (<140/95 mmHg) was achieved in 33% with captopril, 29% with hydralazine, 17% with nifedipine, and 10% with placebo. Compared to other agents, captopril increased serum potassium (value not reported; P=0.01). Mean changes in serum cholesterol: captopril -0.2 mmol/L, hydralazine -0.8 mmol/L, nifedipine -0.2 mmol/L, and placebo 0.2 mmol/L (P<0.001). Side effects did not differ significantly between the groups. Withdrawal

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				rates: captopril 15%, hydralazine 24%, nifedipine 22%, and placebo 3% (P=0.04).
Julien et al.[30] (1990) Captopril 150 to 300 mg/day vs minoxidil 7.5 to 30 mg/day	DB, PG, RCT Male patients with left ventricular hypertrophy and essential HTN with DBP >95 mmHg who were taking metoprolol 200 mg/day and furosemide 80 mg/day	N=34 6 months	Primary: Blood pressure changes and left ventricular hypertrophy changes as seen on electrocardiogram Secondary: Not reported	Primary: Blood pressure decreased significantly in both groups; captopril (163/102 to 135/89 mmHg) and minoxidil (160/99 to 137/87 mmHg; P<0.001). Electrocardiogram criteria for left ventricular hypertrophy improved with captopril only with a decrease in intraventricular septum, posterior wall, and left ventricular mass (17.4 to 15.9 mm; P<0.05, 14.5 to 13.4 mm; P<0.05 and 236 to 198 g/m^2; P<0.001, respectively). No changes on electrocardiogram criteria with minoxidil. Secondary: Not reported
McAreavey et al.[31] (1984) Hydralazine 12.5 mg QD up to 100 mg BID vs labetalol 200 mg QD up to 1,600 mg BID vs methyldopa 125 mg QD up to 1,000 mg BID vs prazosin 0.5 mg	DB, PG, RCT Patients with inadequately controlled HTN while receiving atenolol 100 mg/day and bendrofluazide* 5 mg/day	N=238 6 months	Primary: Comparative safety and efficacy, target blood pressure <140/95 mm Hg Secondary: Not reported	Primary: Target blood pressure was reached in 25% of patients receiving hydralazine, 23% of patients receiving minoxidil, 19% of patients receiving prazosin, 17% of patients receiving methyldopa and zero percent of patients receiving placebo (P values not reported). Labetalol had the highest withdrawal rate compared to the other treatments with 78% (P<0.05). Minoxidil had the second highest withdrawal rate with 57% (P<0.05), due to fluid retention. There were no significant differences in withdrawal rates among the other treatments. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD up to 10 mg BID vs placebo Minoxidil as add-on therapy was given to men only.				
Materson et al.[32] (1990) Hydralazine 25, 50 or 100 mg BID vs metoprolol 50, 100 or 200 mg BID vs methyldopa 250, 500 or 1,000 mg BID vs reserpine 0.05, 0.10 or 0.25 mg QD All patients received HCTZ 25 to 100 mg QD.	DB, MC, RCT Men ≥60 years with HTN not currently receiving antihypertensive therapy with a DBP 90 to 114 mm Hg and a SBP <240 mm Hg; or a DBP <100 mm Hg and a SBP <240 mm Hg if currently taking antihypertensive therapy and the blood pressure criteria was met after ≥2 weeks without medication	N=690 12 months	Primary: Average reduction in SBP, DBP, the number of patients achieving the goal blood pressure and the average change in heart rate Secondary: Rates of drug intolerances and incidence of adverse effects	Primary: A total of 269 patients were uncontrolled with HCTZ therapy alone and were randomized to receive hydralazine (n=68), methyldopa (n=71), metoprolol (n=65), or reserpine (n=65). A total of 213 of the 269 patients achieved goal blood pressure with the addition of one of four therapies was added to HCTZ and entered the 6 month maintenance phase; 186 patients completed the maintenance phase. Across all four add-on therapies, there was an additional average reduction in blood pressure of 13.1/10.6 mm Hg. The average reduction in SBP (mm Hg)±SD from baseline to endpoint for hydralazine, methyldopa, metoprolol, and reserpine add-on therapies was: -11.5±10.1 (P<0.001), -15.0±13.7 (P<0.001), -13.0±15.4 (P<0.001), and -12.7±11.5 (P<0.001), respectively. There was no statistically significant difference in SBP reductions among the different groups (P=0.43). The average reduction in DBP (mm Hg)±SD from baseline to endpoint for hydralazine, methyldopa, metoprolol, and reserpine add-on therapies was: -11.3±5.9 (P<0.001), -10.6±6.3 (P<0.001), -10.6±6.7 (P<0.001), and -9.8±6.3 (P<0.001), respectively. There was no statistically significant difference in DBP reductions among the different groups (P=0.59). The average change in heart rate (beats per minute) ±SD from baseline to endpoint for hydralazine, methyldopa, metoprolol, and reserpine add-on therapies was: 1.4±10.5 (P value not significant), -1.6±9.3 (P value not significant), 15.9±11.9 (P<0.05), and -7.9±10.7 (P<0.05), respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was a statistically significant difference in change in heart rate among the different groups (P<0.001). The percentage of patients achieving the goal blood pressure at endpoint in the hydralazine, methyldopa, metoprolol, and reserpine groups was: 85.3, 81.7, 76.9, and 72.3%, respectively (P=0.28). Secondary: Drug intolerance, defined as adverse effects prompting dose reduction or discontinuation, was present in 23.3% of those not achieving goal blood pressure compared to 2.8% of those achieving the goal blood pressure (P<0.001). This was statistically significant in the hydralazine, methyldopa, and metoprolol groups, but not the reserpine group. There were 27 (10%) study terminations due to adverse drug events: hydralazine (n=3), methyldopa (n=8), metoprolol (n=9), and reserpine (n=7). There were 2 study terminations in the methyldopa-treated group and 1 in the reserpine group due to depression. The overall incidence of volunteered moderate or severe adverse effects, not prompting study termination was significantly greater (P<0.01) with methyldopa (31%) and hydralazine (25%) compared to reserpine (15%) or metoprolol (9%).

*Synonym for bendroflumethiazide.
Drug regimen abbreviations: BID=twice daily, QD=once daily, TID=three times daily
Study abbreviations: AC=active controlled, DB=double blind, ES=extended study, MC=multicenter, OL=open label, PC=placebo controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial
Miscellaneous abbreviations: ACE=angiotensin converting enzyme, CI=confidence interval, DBP=diastolic blood pressure, FDA=Food and Drug Administration, HCTZ=hydrochlorothiazide, HR=hazard ratio, HTN=hypertension, ISDN=isosorbide dinitrate, LVEF=left ventricular ejection fraction, LVET=left ventricular ejection time, NYHA=New York Heart Association, PEP=pre-ejection period, SBP=systolic blood pressure, SD=standard deviation, SVR=systemic vascular resistance

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 10. Relative Cost of the Direct Vasodilators

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Hydralazine	injection, tablet	N/A	N/A	$
Minoxidil	tablet	N/A	N/A	$
Combination Products				
Isosorbide dinitrate and hydralazine	tablet	BiDil®*	$$$$$	$$$$

*Generic is available in at least one dosage form or strength.
N/A=not available

X. Conclusions

Hydralazine and minoxidil are approved for the treatment of hypertension, and both agents are available in a generic formulation.[1,2,4] There are several national and international organizations that have published guidelines on the treatment of hypertension. Most of the guidelines do not provide recommendations on the use of the oral direct vasodilators.[5-11] Thiazide-type diuretics are frequently recommended as initial therapy in patients with uncomplicated hypertension. According to the National Heart, Lung, and Blood Institute's Eighth Report of The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8), thiazide-type diuretics should be utilized first-line for most patients with hypertension, either alone or in combination with another antihypertensive from a different medication class (e.g., ACE inhibitors, ARBs, β-

blockers, calcium channel blockers).[5] Several guidelines consistently recommend that the selection of an antihypertensive agent be based on compelling indications for use.[5-11] Most patients will require more than one antihypertensive medication to achieve blood pressure goals.[5-11] Clinical trials have demonstrated that hydralazine and minoxidil are effective for the treatment of hypertension when added to existing therapy in patients whose blood pressure is inadequately controlled. There are limited head-to-head trials comparing the direct vasodilators.[28-32] These agents are associated with several potentially severe adverse effects, which limits their use in the treatment of hypertension.[1,2]

Hydralazine and isosorbide dinitrate (administered as single entity products) have been used off-label to treat heart failure for many years. The combination of these agents has been shown to reduce mortality compared to placebo in patients receiving standard therapy with digoxin and diuretics.[25] However, when hydralazine and isosorbide dinitrate were directly compared to an ACE inhibitor, mortality was significantly lower in the ACE inhibitor group.[26] Treatment guidelines for the management of heart failure currently recommend the use of hydralazine and an oral nitrate in patients who do not tolerate an ACE inhibitor or ARB.[13-18] The fixed-dose combination of isosorbide dinitrate and hydralazine is FDA-approved for the treatment of heart failure as an adjunct to standard therapy in self-identified black patients.[3] In the A-HeFT trial, the use of this combination product improved mortality, prolonged time to hospitalization for heart failure, and improved functional status compared to placebo. The patients in this trial were also receiving standard heart failure therapy prior to enrollment (ACE inhibitors, angiotensin II receptor antagonists, β-blockers, diuretics, digoxin, spironolactone).[3,20-23] The Heart Failure Society of America and the American College of Cardiology Foundation/American Heart Association recommend the use of the fixed-dose combination of isosorbide dinitrate and hydralazine in African American patients with NYHA functional class III or IV heart failure who are on a standard regimen including an ACE inhibitor (or ARB) and a β-blocker.[14] Both hydralazine and isosorbide dinitrate are available generically; however, generic hydralazine is not available in a strength equivalent to the fixed-dose combination product.[1-4]

Therefore, all brand direct vasodilators within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use. The fixed-dose combination of isosorbide dinitrate and hydralazine (BiDil®) should be available through the medical justification portion of the prior authorization process as an adjunct to standard heart failure therapy in self-identified black patients.

XI. Recommendations

No brand direct vasodilator is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Peripheral Adrenergic Inhibitors
AHFS Class 240832
May 8, 2024

I. Overview

In 2016, reserpine was discontinued. Currently, there are no drugs classified by AHFS as peripheral adrenergic inhibitors.

II. Conclusions

There are no drugs available in the peripheral adrenergic inhibitor class (AHFS Class 240832).

III. Recommendations

No brand peripheral adrenergic inhibitor is recommended for preferred status. Alabama Medicaid should continue to include AHFS Class 240832 in the PDL screening process. If new outpatient peripheral adrenergic inhibitors are added, it is recommended that this class be re-reviewed at that time.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Hypotensive Agents, Miscellaneous
AHFS Class 240892
May 8, 2024

I. Overview

Mecamylamine was one of the first oral antihypertensive agents, introduced in the mid-1950s under the trade name Inversine®. It was withdrawn from the market in 2009 due to increased competition of antihypertensive drugs and decreasing use of the agent. In March 2013, mecamylamine was issued FDA approval and re-entered the market under the name of Vecamyl®.[1,2] Mecamylamine, a ganglionic blocker and secondary amine, inhibits acetylcholine at the autonomic ganglia. This causes blood vessel dilation and an increase in peripheral blood flow resulting in a decrease in blood pressure. Additionally, it blocks central nicotinic cholinergic receptors. Mecamylamine use has diminished due to its ganglionic side effects at antihypertensive doses.[1,3,4]

The miscellaneous hypotensive agents that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. This class was last reviewed in May 2022.

Table 1. Miscellaneous Hypotensive Agents Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Mecamylamine	tablet	Vecamyl®	none

PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

The miscellaneous hypotensive agents are not included in the treatment guidelines and there are no specific recommendations for this drug.

III. Indications

Food and Drug Administration (FDA)-approved indications for the miscellaneous hypotensive agents are listed in Table 2. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 2. FDA-Approved Indications for the Miscellaneous Hypotensive Agents[3]

Indication	Mecamylamine
Management of moderately severe to severe essential hypertension and in uncomplicated cases of malignant hypertension.	✔

IV. Pharmacokinetics

The pharmacokinetic parameters for miscellaneous hypotensive agents are summarized in Table 3.

Table 3. Pharmacokinetic Parameters of the Miscellaneous Hypotensive Agents[4]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Elimination (%)	Half-life (hours)	Active Metabolites
Mecamylamine	Not reported*	Not reported	Renal (100)	24	Not reported

*It is noted that mecamylamine is readily absorbed from the gastrointestinal tract

V. Drug Interactions

There are no reported drug interactions of major or moderate significance with the miscellaneous hypotensive agent, mecamylamine, although the package insert states that patients receiving antibiotics and sulfonamides generally should not be treated with ganglion blockers.[3,5] Additionally, the action of mecamylamine may be amplified by anesthesia, other antihypertensive agents, and alcohol. The mechanism of these interactions and specific drug agents are not specified.[3]

VI. Adverse Drug Events

The most common adverse reactions reported with the miscellaneous hypotensive agents are noted in Table 4.

Table 4. Adverse Events (%) Reported with the Miscellaneous Hypotensive Agents[3]

Adverse Events	Mecamylamine
Cardiovascular	
Orthostatic dizziness	✔
Postural hypotension	✔
Syncope	✔
Central Nervous System	
Choreiform movements	✔
Convulsions	✔
Mental aberrations	✔
Paresthesias	✔
Tremor	✔
Gastrointestinal	
Anorexia	✔
Constipation	✔
Dry mouth	✔
Glossitis	✔
Ileus	✔
Nausea	✔
Vomiting	✔
Respiratory	
Fibrosis	✔
Interstitial pulmonary edema	✔
Urogenital	
Decreased libido	✔
Impotence	✔
Urinary retention	✔
Other	
Blurred vision	✔
Dilated pupils	✔
Fatigue	✔
Sedation	✔
Weakness	✔

VII. Dosing and Administration

The usual dosing regimens for the miscellaneous hypotensive agents are summarized in Table 5.

Table 5. Usual Dosing for the Miscellaneous Hypotensive Agents[3]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Mecamylamine	Management of moderately severe to severe essential hypertension and in uncomplicated cases of malignant hypertension: Tablet: initial, 2.5 mg twice daily (titrate in increments of 2.5 mg with at least two day intervals); average, 25 mg daily, in three divided doses (some patients may respond to as little as 2.5 mg daily; however, some patients may require two to four doses or greater in severe cases when consistent control is difficult to achieve); partial tolerance may develop requiring daily dosage increases	Safety and effectiveness have not been established.	Tablet: 2.5 mg

VIII. Effectiveness

A thorough literature search from 1966 to the present failed to retrieve any clinical studies evaluating the safety and effectiveness of mecamylamine for the treatment of hypertension. The initial clinical trials were conducted in the 1950s. These trials established the drug's efficacy and side effect profile in patients with severe hypertension.[1]

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 10. Relative Cost of the Miscellaneous Hypotensive Agents

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Mecamylamine	tablet	Vecamyl®	$$$$$	N/A

*Generic is available in at least one dosage form or strength.
N/A=not available

X. Conclusions

Although the clinical literature reports that mecamylamine is effective for the management of moderate-to-severe hypertension, its clinical utility is minimal due to its adverse events profile and the availability of newer and more effective agents. Current hypertension treatment guidelines do not mention mecamylamine as a first-line or alternative agent for the treatment of hypertension. Therefore, all brand miscellaneous hypotensive agents within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand miscellaneous hypotensive agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Alpha-Adrenergic Blocking Agents
AHFS Class 242000
May 8, 2024

I. Overview

The alpha-adrenergic blocking agents are approved for the treatment of benign prostatic hyperplasia (BPH) and hypertension.[1-6] However, the use of these agents for the treatment of hypertension is somewhat limited due to adverse events. They can cause postural hypotension, reducing the standing systolic blood pressure by more than 10 mm Hg. Syncope with sudden loss of consciousness can also occur, especially with the first few doses, rapid dose increases, or the addition of another antihypertensive agent to the treatment regimen. Unlike diuretics and β-adrenergic blocking agents, α-adrenergic blocking agents do not adversely affect lipids. They have been shown to reduce total cholesterol by 3 to 5% and triglycerides by 3 to 4%, as well as increase high-density lipoprotein cholesterol.[7] The α-adrenergic blocking agents are more commonly used to relieve symptoms of BPH, which is characterized by an enlargement of the prostate gland. BPH is associated with lower urinary tract symptoms, such as frequent daytime urination, nocturia, a sensation of incomplete bladder emptying, and a hesitant, weak, or intermittent urinary stream.[8,9]

The α-adrenergic blocking agents competitively inhibit postsynaptic α_1-adrenergic receptors, which are classified into three subtypes: α_{1A}, α_{1B}, and α_{1D}.[10-13] These receptors are located in the smooth muscle cell membrane of the peripheral blood vessels, as well as in various nonvascular smooth muscle and non-muscular tissues.[11-15] The α-adrenergic blocking agents lower blood pressure by acting peripherally to dilate the blood vessels. They also cause rapid relaxation of smooth muscle in the bladder neck, prostate capsule, and prostatic urethra.[14,16]

The α-adrenergic blocking agents that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All of the products are available in a generic formulation. This class was last reviewed in May 2022.

Table 1. Alpha-Adrenergic Blocking Agents Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Doxazosin	extended-release tablet, tablet	Cardura®*, Cardura XL®	doxazosin
Prazosin	capsule	Minipress®*	prazosin
Terazosin	capsule	N/A	terazosin

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List
N/A=Not available

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the α-adrenergic blocking agents are summarized in Table 2.

Table 2. Treatment Guidelines Using the Alpha-Adrenergic Blocking Agents

Clinical Guideline	Recommendations
Eighth Joint National Committee (JNC 8): **2014 Evidence-based Guideline for the Management of High Blood Pressure in Adults (2014)**[17]	• Pharmacologic treatment should be initiated in patients ≥60 years of age to lower blood pressure at systolic blood pressure ≥150 mm Hg or diastolic blood pressure ≥90 mm Hg and to a goal systolic blood pressure <150 mm Hg and goal diastolic blood pressure <90 mm Hg. Adjustment of treatment is not necessary if treatment results in lower blood pressure and treatment is well tolerated and without adverse effects on health or quality of life. • In patients <60 years of age, pharmacologic treatment should be initiated to lower blood pressure at diastolic blood pressure ≥90 mm Hg to a goal diastolic blood pressure <90 mm Hg. • In patients <60 years of age, pharmacologic treatment should be initiated to

Clinical Guideline	Recommendations
	lower blood pressure at systolic blood pressure ≥150 mm Hg to a goal diastolic blood pressure <140 mm Hg. • For patients ≥18 years of age with chronic kidney disease or diabetes, pharmacologic treatment should be initiated to lower blood pressure at systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg and to a goal systolic blood pressure <140 mm Hg and goal diastolic blood pressure <90 mm Hg. • Initial antihypertensive treatment for the general nonblack population, including those with diabetes, should include thiazide-type diuretic, calcium channel blocker (CCB), ACE inhibitor, or ARB. • Initial antihypertensive treatment for the general black population, including those with diabetes, should include thiazide-type diuretic or CCB. • For patients ≥18 years of age with chronic kidney disease regardless of race or diabetes status, initial (or add-on) treatment should include an ACE inhibitor or ARB to improve kidney outcomes. • The main goal of antihypertensive treatment is to attain and maintain goal blood pressure. • If goal blood pressure is not attained within a month of treatment, the dose of the initial drug should be increased or second drug from the thiazide-type diuretic, CCB, ACE inhibitor, or ARB classes should be added. • If goal is not achieved with two drugs, a third drug from the thiazide-type diuretic, CCB, ACE inhibitor, or ARB classes should be added. • An ACE inhibitor and ARB should not be used together. • Antihypertensive classes can be used if the patient is unable to achieve goal blood pressure with three agents or had a contraindication to a preferred class. • If blood pressure is not able to be achieved or in complicated patients, referral to a hypertension specialist may be indicated.
International Society of Hypertension: **Global Hypertension Practice Guidelines (2020)[18]**	<u>Lifestyle modifications</u> • Lifestyle modification is the first line of antihypertensive treatment. • Salt reduction: Reduce salt added when preparing foods, and at the table. Avoid or limit consumption of high salt foods such as soy sauce, fast foods and processed food including breads and cereals high in salt. • Healthy diet: Eating a diet that is rich in whole grains, fruits, vegetables, polyunsaturated fats and dairy products and reducing food high in sugar, saturated fat and trans fats, such as the DASH diet. • Healthy drinks: Moderate consumption of coffee, green and black tea. Other beverages that can be beneficial include karkadé (hibiscus) tea, pomegranate juice, beetroot juice and cocoa. • Moderation of alcohol consumption: The recommended daily limit for alcohol consumptions is 2 standard drinks for men and 1.5 for women (10 g alcohol/standard drink). Avoid binge drinking. • Weight reduction: Body weight control is indicated to avoid obesity. Particularly abdominal obesity should be managed. Ethnic-specific cut-offs for BMI and waist circumference should be used. Alternatively, a waist-to-height ratio <0.5 is recommended for all populations. • Smoking cessation: Smoking is a major risk factor for cardiovascular disease (CVD), COPD and cancer. Smoking cessation and referral to smoking cessation programs are advised. • Regular physical activity: Studies suggest that regular aerobic and resistance exercise may be beneficial for both the prevention and treatment of hypertension. Moderate intensity aerobic exercise (walking, jogging, cycling, yoga, or swimming) for 30 minutes on five to seven days per week Strength training also can help reduce blood pressure. Performance of resistance/strength exercises on two to three days per week. • Reduce stress and induce mindfulness: Stress should be reduced and

Clinical Guideline	Recommendations
	mindfulness or meditation introduced into the daily routine. • Reduce exposure to air pollution and cold temperature: Evidence from studies support a negative effect of air pollution on blood pressure in the long-term. <u>Pharmacological Treatment</u> • Ideal characteristics of drug treatment o Treatments should be evidence-based in relation to morbidity/mortality prevention. o Use a once-daily regimen which provides 24-hour blood pressure control. o Treatment should be affordable and/or cost-effective relative to other agents. o Treatments should be well-tolerated. o Evidence of benefits of use of the medication in populations to which it is to be applied. • General scheme for drug treatment o Lifestyle modification is the first line of antihypertensive treatment. o Grade 1 hypertension (BP 140 to 159/ 90 to 99): Immediate drug treatment in high-risk patients or those with CVD, chronic kidney disease (CKD), diabetes mellitus (DM), or hypertension-mediated organ damage (HMOD). Drug treatment after three to six months of lifestyle intervention if BP still not controlled in low to moderate risk patients. o Grade 2 hypertension (BP ≥160/100): Immediate drug treatment in all patients. • Core drug-treatment strategy o Step 1: Dual low-dose combination (ACE inhibitor or ARB plus dihydropyridine-calcium channel blockers (DHP-CCB)); consider monotherapy in low-risk grade 1 hypertension or in very old (≥80 years) or frail patients; consider ACE/ARB plus thiazide-like diuretic in post-stroke, very elderly, incipient HF, or CCB intolerance; consider ACE/ARB plus DHP-CCB or DHP-CCB plus thiazide-like diuretics in black patients. o Step 2: Dual full-dose combination (ACE inhibitor or ARB plus DHP-CCB); consider monotherapy in low-risk grade 1 hypertension or in very old (≥80 years) or frail patients; consider ACE/ARB plus thiazide-like diuretic in post-stroke, very elderly, incipient HF, or CCB intolerance. o Step 3: Triple combination (ACE/ARB plus DHP-CCB plus thiazide-like diuretic). o Step 4, resistant hypertension: triple combination plus spironolactone or other drug, alternatives include amiloride, doxazosin, eplerenone, clonidine, or β-blocker. Caution with spironolactone or other potassium sparing diuretics when estimated GFR <45 mL/min/1.73m^2 or K+ >4.5 mmol/L. o Consider β-blockers at any treatment step when there is a specific indications for their use, e.g., heart failure, angina, post-MI, atrial fibrillation, or younger women planning pregnancy or pregnant.
Hypertension Canada: **2020 Guidelines for the Prevention, Diagnosis, Risk Assessment, and Treatment of Hypertension in Adults and Children**	<u>Indications for drug therapy for adults with hypertension without compelling indications for specific agents</u> • Antihypertensive therapy should be prescribed for average diastolic blood pressure (DBP) measurements of ≥100 mmHg or average systolic blood pressure (SBP) measurements of ≥160 mmHg in patients without macrovascular target organ damage or other cardiovascular risk factors. • Antihypertensive therapy should be strongly considered for average DPB readings ≥90 mmHg or for average SBP readings ≥140 mmHg in the presence

Clinical Guideline	Recommendations
(2020)[19]	of macrovascular target organ damage or other independent cardiovascular risk factors. • For high-risk patients, aged 50 years or older, with SBP levels ≥130 mmHg, intensive management to target a SBP <120 mmHg should be considered. Patient selection for intensive management is recommended and caution should be taken in certain high-risk groups. <u>Indications for drug therapy for adults with diastolic and with or without systolic hypertension</u> • Initial therapy should be with either monotherapy or single pill combination (SPC). o Recommended monotherapy choices are: ▪ A thiazide/thiazide-like diuretic, with longer-acting diuretics preferred; ▪ A β-blocker (in patients <60 years of age); ▪ An angiotensin-converting enzyme (ACE) inhibitor (in nonblack patients); ▪ An angiotensin receptor blocker (ARB); or ▪ A long-acting calcium channel blocker (CCB). o Recommended SPC choices are those in which an ACE inhibitor is combined with a CCB, ARB with a CCB, or ACE inhibitor or ARB with a diuretic. o Hypokalemia should be avoided in patients treated with thiazide/thiazide-like diuretic monotherapy. • Additional antihypertensive drugs should be used if target BP levels are not achieved with standard-dose monotherapy. Add-on drugs should be chosen from first-line choices. Useful choices include a thiazide/thiazide-like diuretic or CCB with either: ACE inhibitor, ARB, or β-blocker. Caution should be exercised in combining a nondihydropyridine CCB and a β-blocker. The combination of an ACE inhibitor and an ARB is not recommended. • If BP is still not controlled with a combination of two or more first-line agents, or there are adverse effects, other antihypertensive drugs may be added. • Possible reasons for poor response to therapy should be considered. • α-Blockers are not recommended as first-line agents for uncomplicated hypertension; β-blockers are not recommended as first-line therapy for uncomplicated hypertension in patients ≥60 years of age; and ACE inhibitors are not recommended as first-line therapy for uncomplicated hypertension in black patients. However, these agents may be used in patients with certain comorbid conditions or in combination therapy. <u>Indications for drug therapy for adults with isolated systolic hypertension</u> • Initial therapy should be single-agent therapy with a thiazide/thiazide-like diuretic, a long-acting dihydropyridine CCB, or an ARB. If there are adverse effects, another drug from this group should be substituted. Hypokalemia should be avoided in patients treated with thiazide/thiazide-like diuretic monotherapy. • Additional antihypertensive drugs should be used if target BP levels are not achieved with standard-dose monotherapy. Add-on drugs should be chosen from first-line options. • If BP is still not controlled with a combination of two or more first-line agents, or there are adverse effects, other classes of drugs (such as α-blockers, ACE inhibitors, centrally acting agents, or nondihydropyridine CCBs) may be combined or substituted. • Possible reasons for poor response to therapy should be considered. • α-Blockers are not recommended as first-line agents for uncomplicated isolated systolic hypertension; and β-blockers are not recommended as first-line therapy for isolated systolic hypertension in patients ≥60 years of age. However, both

Clinical Guideline	Recommendations
	agents may be used in patients with certain comorbid conditions or in combination therapy. Guidelines for hypertensive patients with coronary artery disease (CAD) • For most hypertensive patients with CAD, an ACE inhibitor or ARB is recommended. • For hypertensive patients with CAD, but without coexisting systolic heart failure, the combination of an ACE inhibitor and ARB is not recommended. • For high-risk hypertensive patients, when combination therapy is being used, choices should be individualized. The combination of an ACE inhibitor and a dihydropyridine CCB is preferable to an ACE inhibitor and a thiazide/thiazide-like diuretic in selected patients. • For patients with stable angina pectoris but without previous heart failure, myocardial infarction, or coronary artery bypass surgery, either a β-blocker or CCB can be used as initial therapy. • Short-acting nifedipine should not be used. • When decreasing SBP to target levels in patients with established CAD (especially if isolated systolic hypertension is present), be cautious when the DBP is ≤60 mmHg because of concerns that myocardial ischemia might be exacerbated, especially in patients with left ventricular hypertrophy (LVH). Guidelines for patients with hypertension who have had a recent myocardial infarction • Initial therapy should include a β-blocker as well as an ACE inhibitor. • An ARB can be used if the patient is intolerant of an ACE inhibitor. • CCBs may be used in patients after myocardial infarction when β-blockers are contraindicated or not effective. Nondihydropyridine CCBs should not be used when there is heart failure, evidenced by pulmonary congestion on examination or radiography. Treatment of hypertension in association with heart failure • In patients with systolic dysfunction (ejection fraction <40%), ACE inhibitors and β-blockers are recommended for initial therapy. Aldosterone antagonists (mineralocorticoid receptor antagonists) may be combined in treatment for patients with a recent cardiovascular hospitalization, acute myocardial infarction, elevated B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide level, or New York Heart Association (NYHA) Class II-IV symptoms. Careful monitoring for hyperkalemia is recommended when combining an aldosterone antagonist with ACE inhibitor or ARB treatment. Other diuretics are recommended as additional therapy if needed. Beyond considerations of BP control, doses of ACE inhibitors or ARBs should be titrated to those reported to be effective in trials unless adverse effects become manifest. • An ARB is recommended if ACE inhibitors are not tolerated. • A combination of hydralazine and isosorbide dinitrate is recommended if ACE inhibitors and ARBs are contraindicated or not tolerated. • For hypertensive patients whose BP is not controlled, an ARB may be combined with an ACE inhibitor and other antihypertensive drug treatment. Careful monitoring should be used if combining an ACE inhibitor and an ARB because of potential adverse effects such as hypotension, hyperkalemia, and worsening renal function. Additional therapies may also include dihydropyridine CCBs. • An angiotensin receptor-neprilysin inhibitor (ARNI) should be used in place of an ACE inhibitor or ARB for patients with HFrEF (<40%) who remain symptomatic despite treatment with appropriate dose of guideline directed HF therapy. Eligible patients must have a serum potassium <5.2 mmol/L, an eGFR

Clinical Guideline	Recommendations

	≤30 mL/min/1.73m^2 and close surveillance of serum potassium and creatinine.
	
	<u>Treatment of hypertension in association with stroke</u>
	• BP management in acute ischemic stroke (onset to 72 hours)
	  o Please refer to Stroke Best Practice recommendations.
	• BP management after acute ischemic stroke
	  o Strong consideration should be given to the initiation of antihypertensive therapy after the acute phase of a stroke or transient ischemic attack.
	  o After the acute phase of a stroke, BP-lowering treatment is recommended to a target of consistently <140/90 mmHg.
	  o Treatment with an ACE inhibitor and thiazide/thiazide-like diuretic combination is preferred.
	  o For patients with stroke, the combination of an ACE inhibitor and ARB is not recommended.
	• BP management in hemorrhagic stroke (onset to 72 hours)
	  o Please refer to Stroke Best Practice recommendations.
	
	<u>Treatment of hypertension in association with LVH</u>
	• Hypertensive patients with LVH should be treated with antihypertensive therapy to decrease the rate of subsequent cardiovascular events.
	• The choice of initial therapy can be influenced by the presence of LVH. Initial therapy can be drug treatment using ACE inhibitors, ARBs, long-acting CCBs, or thiazide/thiazide-like diuretics. Direct arterial vasodilators such as hydralazine or minoxidil should not be used.
	
	<u>Treatment of hypertension in association with nondiabetic chronic kidney disease</u>
	• Individualize BP targets in patients with chronic kidney disease. Consider intensive targets (SBP <120 mmHg) in appropriate patients.
	• For patients with hypertension and proteinuric chronic kidney disease (urinary protein >150 mg per 24 hours or albumin to creatinine ratio >30 mg/mmol), initial therapy should be an ACE inhibitor or an ARB if there is intolerance to ACE inhibitors.
	• In most cases, combination therapy with other antihypertensive agents might be needed to reach target BP levels.
	• The combination of an ACE inhibitor and ARB is not recommended for patients with nonproteinuric chronic kidney disease.
	
	<u>Treatment of hypertension in association with renovascular disease</u>
	• Patients with hypertension attributable to atherosclerotic renal artery stenosis should be primarily medically managed because renal angioplasty and stenting offers no benefit over optimal medical therapy alone.
	• Renal artery angioplasty and stenting for atherosclerotic hemodynamically significant renal artery stenosis could be considered for patients with uncontrolled hypertension resistant to maximally tolerated pharmacotherapy, progressive renal function loss, and acute pulmonary edema.
	• Patients with confirmed renal fibromuscular dysplasia (FMD) should be referred to a hypertension specialist.
	• Renal artery angioplasty without stenting is recommended for treatment of FMD-related renal artery stenosis. Stenting is not recommended unless needed because of a periprocedural dissection. Surgical revascularization should be considered in cases of complex lesions less amendable to angioplasty, stenosis associated with complex aneurysm, and restenosis despite two unsuccessful attempts of angioplasty.
	
	<u>Treatment of hypertension in association with diabetes mellitus</u>

Clinical Guideline	Recommendations
	• Persons with diabetes mellitus should be treated to attain SBP of <130 mmHg and DBP of <80 mmHg. • For persons with cardiovascular or kidney disease, including microalbuminuria, or with cardiovascular risk factors in addition to diabetes and hypertension, an ACE inhibitor or an ARB is recommended as initial therapy. • For persons with diabetes and hypertension not included in other guidelines in this section, appropriate choices include (in alphabetical order): ACE inhibitors, ARBs, dihydropyridine CCBs, and thiazide/thiazide-like diuretics. • If target BP levels are not achieved with standard-dose monotherapy, additional antihypertensive therapy should be used. For persons in whom combination therapy with an ACE inhibitor is being considered, a dihydropyridine CCB is preferable to a thiazide/thiazide-like diuretic. <u>Resistant hypertension</u> • Resistant hypertension is defined as BP above target despite three or more BP-lowering drugs at optimal doses preferably including a diuretic (and usually a renin-angiotensin-aldosterone system blocker and a CCB. • Accurate office and out-of-office BP measurement is essential. • Other reasons for apparent resistant hypertension should be eliminated before diagnosing true resistant hypertension, including nonadherence, white coat effect, and secondary hypertension. • Pharmacotherapy with the additional use of spironolactone, bisoprolol, doxazosin, amiloride, eplerenone, or clonidine with the baseline regimen decreases BP significantly, with the greatest BP-lowering shown with spironolactone. • Patients with resistant hypertension should be referred to providers with expertise in diagnosis and management of hypertension. <u>Hypertension and pediatrics</u> • BP should be measured regularly in children three years of age or older; the auscultatory method is the gold-standard at present. • Initial therapy should be monotherapy, with an ACE inhibitor or ARB (not first-line in black children), or a long-acting dihydropyridine CCB. • The treatment t goal is systolic and diastolic office BP and/or ABPM < 95th percentile or <90th percentile in children with risk factors or target organ damage. • Complex cases should be referred to an expert in pediatric hypertension. <u>Hypertension and pregnancy</u> • Up to 7% of pregnancies are complicated by a hypertensive disorder of pregnancy, and approximately 5% of women will have chronic hypertension when they become pregnant. • The prevalence of hypertension in pregnancy is expected to increase with women becoming pregnant later in their reproductive years and the increasing prevalence of cardiovascular comorbidities such as increased preconception body mass index and maternal diabetes. • The possibility of pregnancy should be considered when managing women with hypertension who are of reproductive age. • Preconception counselling should be offered to all women with hypertension who are considering pregnancy. • ACE inhibitor and ARB therapy should be avoided before conception and during pregnancy unless there is a compelling indication for their use (i.e., proteinuric kidney disease). • Hypertension during pregnancy can increase the risk of adverse maternal and fetal outcomes, including an increased risk of preeclampsia, placental abruption,

Clinical Guideline	Recommendations
	prematurity, small for gestational age infants, stillbirth, and maternal renal and retinal injury, thus generally requires involvement of an interdisciplinary team including obstetrical care providers. • Antihypertensive therapy is recommended for average SBP measurements of ≥140 mmHg or DBP measurements of ≥90 mmHg in pregnant women with chronic hypertension, gestational hypertension, or preeclampsia. Initial antihypertensive therapy should be monotherapy from the following first-line drugs: oral labetalol, oral methyldopa, long-acting oral nifedipine, or other oral b-blockers (acebutolol, metoprolol, pindolol, and propranolol). Other antihypertensive drugs can be considered as second-line drugs including: clonidine, hydralazine, and thiazide diuretics. • Women with severe hypertension with SBP ≥160 mmHg or DBP ≥110 mmHg in pregnancy or postpartum require urgent antihypertensive therapy because it is considered an obstetrical emergency. • Antihypertensive drugs used in breastfeeding women include: labetalol, methyldopa, long-acting nifedipine, enalapril, or captopril.
European Society of Hypertension: **2023 Guidelines for the management of arterial hypertension (2023)[20]**	General recommendations for antihypertensive drug treatment • BP lowering should be prioritized over the selection of specific antihypertensive drug classes because treatment benefit largely originates from BP reduction. • Five major drug classes including, ACE inhibitors, ARBs, β-blockers, CCBs, and Thiazide/Thiazide-like diuretics have effectively reduced blood pressure and cardiovascular events in randomized controlled trials. These drugs and their combinations are recommended as the basis of antihypertensive treatment strategies. • Initiation of therapy with a two-drug combination is recommended for most hypertensive patients. Preferred combinations should comprise a RAS blocker (either an ACE inhibitor or an ARB) with a CCB or thiazide/thiazide-like diuretic. Other combinations of the five major drug classes can be used. • Initiation with monotherapy can be considered in patients with: grade 1 hypertension and low-risk if BP is only marginally elevated (less than 150 mmHg SBP and 95 mmHg DBP) high-normal BP and very high cardiovascular risk, frailty and/or and advance age. • If BP is not controlled with the initial two-drug combination by using the maximum recommended and tolerated dose of the respective components, treatment should be increased to a three-drug combination, usually a RAS blocker plus CCB plus thiazide/thiazide-like diuretic. • If BP is not controlled with a three-drug combination by using the maximum recommended and tolerated dose of the respective components, it is recommended to extend treatment according to the recommendations for resistant hypertension. • The use of single pill combinations should be preferred at any treatment step (i.e. during initiation of therapy with a two-drug combination and at any other step of treatment). • β-blocker should be used at initiation of therapy or at any treatment step as guideline-directed medical therapy (e.g., heart failure with reduced ejection fraction, anti-ischemic therapy in chronic coronary syndromes, heart rate control in atrial fibrillation). • β-blockers can be considered in the presence of several other conditions in which their use can be favorable. • The combination of two RAS blockers is not recommended due to increased risk of adverse events, in particular AKI. True-resistant hypertension • In resistant hypertension, it is recommended to reinforce lifestyle measures. • Drugs that can be considered as additional therapy in patients with resistant

Clinical Guideline	Recommendations
	hypertension are preferably spironolactone (or other MRA), or β-blocker or Alpha-1 blockers or centrally acting agents (clonidine), or amiloride. • Thiazide/thiazide-like diuretics are recommended in resistant hypertension if estimated eGFR is ≥30 mL/min/1.73m^2. • Loop diuretics may be considered in patients with an estimated eGFR < 45 mL/min/1.73m^2 and should be used if eGFR falls below 30 mL/min/1.73m^2. • Chlorthalidone (12.5 to 25 mg once daily) could be used with or without a loop diuretic if eGFR is <30 mL/min/1.73m^2. • Renal deprivation can be considered as an additional treatment option in patients with resistant hypertension if eGFR is >40 mL/min/1.73m^2. • Patients with resistant hypertension should be followed very closely. Follow-up includes periodical ambulatory blood pressure monitoring and assessment of hypertension-mediated organ damage, particularly kidney function and serum potassium levels. Regular use of home blood pressure monitoring and monitoring of drug adherence are desirable.
National Institute for Health and Clinical Excellence: **Hypertension in adults: diagnosis and management (2019)**[21]	<u>Choosing antihypertensive drug treatment (for people with or without type II diabetes)</u> • Where possible, recommend treatment with drugs taken only once a day. • Prescribe non-proprietary drugs where these are appropriate and minimize cost. • Offer people with isolated systolic hypertension (systolic blood pressure ≥160 mmHg) the same treatment as people with both raised systolic and diastolic blood pressure. • Offer antihypertensive drug treatment to women of child-bearing potential with diagnosed hypertension in line with recommendations in this guideline. For women considering pregnancy or who are pregnant or breastfeeding, manage hypertension in line with the recommendations on Management of pregnancy with chronic hypertension and Breastfeeding in 'Hypertension in pregnancy'. • When choosing antihypertensive drug treatment for adults of black African or African-Caribbean family origin, consider an angiotensin II receptor blocker, in preference to an angiotensin-converting enzyme inhibitor. <u>Step one treatment</u> • Patients <55 years of age should be offered a step one antihypertensive with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). • Offer an ACE inhibitor or an ARB to adults starting step 1 antihypertensive treatment who have type II diabetes and are of any age or family origin or those aged <55 years but not of black African or African-Caribbean family origin. • If an ACE inhibitor is not tolerated, offer an ARB. • Do not combine an ACE inhibitor with an ARB for the treatment of hypertension. • Offer a calcium channel blocker (CCB) to adults starting step 1 antihypertensive treatment who are >55 years of age and do not have diabetes and are of black African or African-Caribbean family origin and do not have type II diabetes and of any age. • If a CCB is not suitable, for example because of edema or intolerance, or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic. • If diuretic treatment is to be initiated or changed, offer a thiazide‑like diuretic, such as indapamide in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide. • For adults with hypertension who are already receiving treatment with bendroflumethiazide or hydrochlorothiazide, who have stable, well-controlled blood pressure, continue with their treatment.

Clinical Guideline	Recommendations
	Step two treatment • Before considering next step treatment for hypertension discuss with the person if they are taking their medicine as prescribed and support adherence in line with NICE's guideline on "Medicines adherence: involving patients decisions about prescribed medicines and supporting adherence". • If hypertension is not controlled with a step one treatment of an ACE inhibitor or ARB, offer choice of one of the following drugs in addition to the step one treatment: a CCB or a thiazide-like diuretic. • If hypertension is not controlled in adults taking step one treatment of a CCB, offer the choice of one of the following drugs in addition to the step one treatment: an ACE inhibitor or an ARB or a thiazide-like diuretic. • If hypertension is not controlled in adults of black African or African–Caribbean family origin who do not have type 2 diabetes taking step one treatment, consider an ARB, in preference to an ACE inhibitor, in addition to step one treatment. Step three treatment • Before considering step three treatment, review the person's medications to ensure they are being taken at the optimal doses and discuss adherence (see recommendation under step two). • If hypertension is not controlled in adults taking step two treatment, offer a combination of an ACE inhibitor or ARB and a CCB and a thiazide-like diuretic. Step four treatment • If hypertension is not controlled in adults taking the optimal tolerated doses of an ACE inhibitor or an ARB plus a CCB and a thiazide-like diuretic, regard them as having resistant hypertension. • Before considering further treatment for a person with resistant hypertension, confirm elevated clinic blood pressure measurements using ambulatory or home blood pressure recordings, assess for postural hypotension, and discuss adherence. • For people with confirmed resistant hypertension, consider adding a fourth antihypertensive drug as step four treatment or seeking specialist advice. • Consider further diuretic therapy with low-dose spironolactone for adults with resistant hypertension starting step four treatment who have a blood potassium level of 4.5 mmol/l or less. Use particular caution in people with a reduced estimated glomerular filtration rate because they have an increased risk of hyperkalemia. • When using further diuretic therapy for step four treatment of resistant hypertension, monitor blood sodium and potassium and renal function within one month of starting treatment and repeat as needed thereafter. • Consider an alpha-blocker or beta-blocker for adults with resistant hypertension starting step four treatment who have a blood potassium level of more than 4.5 mmol/l. • If blood pressure remains uncontrolled in people with resistant hypertension taking the optimal tolerated doses of four drugs, seek specialist advice.
American College of Cardiology/American Heart Association Task Force: **Guideline for the Prevention, Detection,**	Initiation of Blood Pressure (BP) Treatment for Overall Cardiovascular Disease (CVD) Risk • Use of BP-lowering medications is recommended for secondary prevention of recurrent CVD events in patients with clinical CVD and an average systolic blood pressure (SBP) ≥130 mmHg or an average diastolic blood pressure (DBP) of ≥80 mmHg and for primary prevention in adults with an estimated 10-

Clinical Guideline	Recommendations
Evaluation, and Management of High Blood Pressure in Adults (2017)[22]	year atherosclerotic cardiovascular disease (ASCVD) risk of ≥10% and an average SBP of ≥130 mmHg or an average ≥80 mmHg. • Use of BP-lowering medication is recommended for primary prevention of CVD in adults with no history of CVD and with an estimated 10-year ASCVD risk <10% and an SBP of ≥140 mmHg or a DBP of ≥90 mmHg. • Simultaneous use of an angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), and/or renin inhibitor is potentially harmful and is not recommended to treat adults with hypertension. • For adults with confirmed hypertension and known CVD or 10-year ASCVD risk of ≥10%, a BP target <130/80 mmHg is recommended. For adults with confirmed hypertension without additional markers of increased CVD risk, a BP target <130/80 mmHg may be reasonable. • For initiation of antihypertensive drug therapy, first-line agents include thiazide diuretics, calcium channel blockers (CCBs), and ACE inhibitors or ARBs. • Initiation of antihypertensive drug therapy with two first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended in adults with stage 2 hypertension and an average BP >20/10 mmHg above their BP target. • Initiation of antihypertensive drug therapy with a single antihypertensive drug is reasonable in adults with stage 1 hypertension and BP goal <130/80 mmHg with dosage titration and sequential addition of other agents to achieve the BP target. <u>Stable Ischemic Heart Disease (SIHD)</u> • In adults with SIHD and hypertension, a BP target <130/80 is recommended. • Adults with SIHD and hypertension (BP ≥130/80 mmHg) should be treated with medications [e.g., guideline-directed medical therapy (GDMT) beta-blockers, ACE inhibitors, or ARBs] for compelling indications [e.g., previous myocardial infarction (MI), stable angina] as first-line therapy, with the addition of other drugs (e.g., dihydropyridine CCBs, thiazide diuretics, and/or mineralocorticoid receptor antagonists) as needed to further control hypertension. • In adults with SIHD with angina and persistent uncontrolled hypertension, the addition of dihydropyridine CCBs to GDMT beta-blockers is recommended. • In adults who have had a MI or acute coronary syndrome, it is reasonable to continue GDMT beta-blockers beyond three years as long-term therapy for hypertension. • Beta-blockers and/or CCBs might be considered to control hypertension in patients with coronary artery disease (CAD) had an MI more than three years ago and have angina. <u>Heart Failure</u> • In adults with increased risk of HF, the optimal BP in those with hypertension should be <130 mmHg. • Adults with HFrEF and hypertension should be prescribed GDMT titrated to attain a BP <130/80 mmHg. • Non-dihydropyridine CCBs are not recommended in the treatment of hypertension in adults with HFrEF. • In adults with HFpEF who present with symptoms of volume overload, diuretics should be prescribed to control hypertension. • Adults with HFpEF and persistent hypertension after management of volume overload should be prescribed ACE inhibitors or ARBs and beta-blockers titrated to attain SBP <130 mmHg. <u>CKD</u> • Adults with hypertension and CKD should be treated to a BP goal <130/80

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	mmHg. • In adults with hypertension and CKD [stage 3 or higher or stage 1 or 2 with albuminuria (≥300 mg/d, or ≥300 mg/g albumin-to-creatinine ratio or the equivalent in the first morning void)], treatment with an ACE inhibitor is reasonable to slow kidney disease progression. Treatment with an ARB may be reasonable if an ACE inhibitor is not tolerated. • After kidney transplantation, it is reasonable to treat patients with hypertension to a BP goal <130/80 mmHg and with a CCB on the basis of improved glomerular filtration rate (GFR) and kidney survival. Cerebrovascular Disease • In adults with intracerebral hemorrhage (ICH) who present with SBP >220 mmHg, it is reasonable to use continuous intravenous (IV) drug infusion and close BP monitoring to lower levels. Immediate lowering of SBP to <140 mmHg in adults with spontaneous ICH who present within six hours of the acute event and have an SBP between 150 mmHg and 220 mmHg is not of benefit to reduce death or severe disability and can be potentially harmful. • Adults with acute ischemic stroke and elevated BP who are eligible for treatment with IV tissue plasminogen activator (tPA) should have their BP slowly lowered to <185/110 mmHg before thrombolytic therapy is initiated. • In adults with an acute ischemic stroke, BP should be <185/110 mmHg before administration of IV tPA and should be maintained below 180/105 mmHg for at least the first 24 hours after initiation drug therapy. • Starting or restarting antihypertensive therapy during hospitalization in patients with BP >140/90 mmHg who are neurologically stable is safe and reasonable to improve long-term BP control, unless contraindicated. • In patient with BP ≥220/120 mmHg who did not receive IV alteplase or endovascular treatment and have no comorbid conditions requiring acute antihypertensive treatment, the benefit of initiating or reinitiating treatment of hypertension within the first 48 to 72 hours is uncertain. It might be reasonable to lower BP by 15% during the first 24 hours after onset of stroke. In patients with BP <220/120 mmHg with the same conditions, initiating or reinitiating treatment of hypertension within the first 48 to 72 hours after an acute ischemic stroke is not effective to prevent death or dependency. • Adults with previously treated stroke or transient ischemic attack should be restarted on antihypertensive treatment after the first few days of the index event to reduce the risk of recurrent stroke and other vascular events. Treatment with a thiazide diuretic, ACE inhibitor, or ARB, or combination treatment consisting of a thiazide diuretic plus ACE inhibitor, is useful. • Adults not previously treated for hypertension who experienced a stroke or transient ischemic attack and have an established BP ≥140/90 mmHg should be prescribed antihypertensive treatment a few days after the index event to reduce the risk of recurrent stroke and other vascular event. • For adults who experience a stroke or transient ischemic attack, selection of specific drugs should be individualized on the basis of patient comorbidities and agent pharmacological class. • For adults who experience a stroke or transient ischemic attack, a BP goal <130/80 mmHg may be reasonable. • For adults with a lacunar stroke, a target SBP goal <130 mmHg may be reasonable. • In adults previously untreated for hypertension who experience an ischemic stroke or transient ischemic attack and have an SBP <140 mmHg and a DBP <90 mmHg, the usefulness of initiating antihypertensive treatment is not well established.

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	Peripheral Artery Disease (PAD) • Adults with hypertension and PAD should be treated similarly to patients with hypertension without PAD. Diabetes Mellitus (DM) • In adults with DM and hypertension, antihypertensive drug treatment should be initiated at a BP of ≥130/80 mmHg with a treatment goal <130/80 mmHg. • In adults with DM and hypertension, all first-line classes of antihypertensive agents (i.e., diuretics, ACE inhibitors, ARBs, and CCBs) are useful and effective. • In adults with DM and hypertension, ACE inhibitors or ARBs may be considered in the presence of albuminuria. Atrial Fibrillation, Valvular Heart Disease, and Aortic disease • Treatment of hypertension can be useful for prevention of recurrence of AF. • In adults with asymptomatic aortic stenosis, hypertension should be treated with pharmacotherapy, starting at a low dose and gradually titrating upward as needed. • In patients with chronic aortic insufficiency, treatment of systolic hypertension with agents that do not slow the heart rate (i.e., avoid beta-blockers) is reasonable. • Beta-blockers are recommended as the preferred antihypertensive agents in patients with hypertension and thoracic aortic disease. Racial and Ethnic Differences in Treatment • In black adults with hypertension but without HF or CKD, including those with DM, initial antihypertensive treatment should include a thiazide-type diuretic or CCB. Two or more antihypertensive medications are recommended to achieve a BP target <130/80 mmHg in most adults with hypertension, especially in black adults with hypertension. Pregnancy • Women with hypertension who become pregnant, or are planning to become pregnant, should be transitioned to methyldopa, nifedipine, and/or labetalol during pregnancy. • Women with hypertension who become pregnant should not be treated with ACE inhibitors, ARBs, or direct renin inhibitors. Older Persons • Treatment of hypertension with an SBP treatment goal <130 mmHg is recommended for noninstitutionalized ambulatory community-dwelling adults (≥65 years of age) with an average SBP of ≥130 mmHg. • For older adults (≥65 years of age) with hypertension and a higher burden of comorbidity and limited life expectancy, clinical judgment, patient preference, and a team-based approach to assess risk/benefit is reasonable for decisions regarding intensity of BP lowering and choice of antihypertensive drugs. Hypertensive Crises • In adults with a hypertensive emergency, admission to an intensive care unit is recommended for continuous monitoring of BP and target organ damage and for parenteral administration of an appropriate agent. • For adults with a compelling condition (i.e., aortic dissection, severe pre-eclampsia or eclampsia, or pheochromocytoma crisis), SBP should be reduced to <140 mmHg during the first hour and to <120 mmHg in aortic dissection. • For adults without a compelling condition, SBP should be reduced by no more

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	than 25% within the first hours; then, if stable, to 160/100 mmHg within the next two to six hours; and then cautiously to normal during the following 24 to 48 hours. Cognitive Decline and Dementia • In adults with hypertension, BP lowering is reasonable to prevent cognitive decline and dementia. Patients Undergoing Surgical Procedures • In patients with hypertension undergoing major surgery who have been on beta-blockers chronically, beta-blockers should be continued. • In patients with hypertension undergoing planned elective major surgery, it is reasonable to continue medical therapy for hypertension until surgery. • In patients with hypertension undergoing major surgery, discontinuation of ACE inhibitors or ARBs perioperatively may be considered. • In patients with planned elective major surgery and SBP ≥180 mmHg or DBP ≥110 mmHg, deferring surgery may be considered. • For patients undergoing surgery, abrupt pre-operative discontinuation of beta-blockers or clonidine is potentially harmful. • Beta-blockers should not be started on the day of surgery in beta-blocker-naïve patients. • Patients with intraoperative hypertension should be managed with IV medications until such time as oral medications can be resumed.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in Blacks (2010)**[23]	• To attain and maintain blood pressure (BP) below target levels, multiple antihypertensive drugs will be required in most hypertensive blacks. • Use of two-drug combination therapy when SBP is >15 mm Hg and/or DBP is >10 mm Hg above goal levels is increasingly recommended as first-line therapy. • Two-drug regimens have generally contained a thiazide-type diuretic; however, the combination of a calcium channel blocker (CCB) with either an ACE inhibitor or an ARB has been shown equally efficacious in BP lowering but with demonstrated superiority (CCB+ACE) for hard clinical outcomes compared with the same ACE inhibitor plus a thiazide-type diuretic. • In secondary prevention patients, the combination therapy should include a drug(s) with the appropriate compelling indications. • Certain classes of antihypertensive medications, specifically diuretics and CCBs, lower BP on average more than β-blockers and renin-angiotensin system (RAS) blockers in black patients when used as monotherapies. • In the absence of compelling indications, when BP is near goal levels, monotherapy with a diuretic or a CCB is preferred. • Lifestyle modifications should be initiated in all patients with hypertension, whether or not pharmacotherapy is planned. • ACE inhibitors or ARBs are recommended as alternative monotherapy options in the treatment of hypertension in blacks. The rationale for their lower tier monotherapy recommendation is because they have consistently achieved lesser average reductions in BP relative to that observed with monotherapy using either a diuretic or CCB.
Kidney Disease Improving Clinical Outcomes Group: **KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney**	Blood pressure measurement • The Work Group recommends standardized office blood pressure (BP) measurement in preference to routine office BP measurements for the management of high BP in adults. • The Work Group suggests that out-of-office BP measurements with ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM) be used to complement standardized office BP readings for the management of high BP.

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Disease (2021)[24]	Lifestyle interventions for lowering BP in patients with chronic kidney disease (CKD) not receiving dialysis • The Work Group suggests targeting a sodium intake <2 grams of sodium per day (or <90 mmol of sodium per day, or <5 grams of sodium chloride per day) in patients with high BP and CKD. • The Work Group suggests that patients with high BP and CKD be advised to undertake moderate-intensity physical activity for a cumulative duration of at least 150 minutes per week, or to a level compatible with their cardiovascular and physical tolerance. BP management in patients with CKD, with or without diabetes, not receiving dialysis • The Work Group suggests that adults with high BP and CKD be treated with a target systolic BP (SBP) of <120 mmHg, when tolerated, using standardized office BP measurement. • The Work Group recommends starting renin-angiotensin-system inhibitors (RASi) (angiotensin-converting enzyme inhibitor [ACEi] or angiotensin II receptor blocker [ARB]) for people with high BP, CKD, and severely increased albuminuria without diabetes. • The Work Group suggests starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately increased albuminuria without diabetes. • The Work Group recommends starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately-to-severely increased albuminuria with diabetes. • The Work Group recommends avoiding any combination of ACEi, ARB, and direct renin inhibitor (DRI) therapy in patients with CKD, with or without diabetes. BP management in kidney transplant recipients • Treat adult kidney transplant recipients with high BP to a target BP of <130 mmHg systolic and <80 mmHg diastolic using standardized office BP measurement. • The Work Group recommends that a dihydropyridine calcium channel blocker (CCB) or an ARB be used as the first-line antihypertensive agent in adult kidney transplant recipients. BP management in children with CKD • The Work Group suggests that in children with CKD, 24-hour mean arterial pressure by ABPM should be lowered to <50th percentile for age, sex, and height.
American Diabetes Association: **Standards of Medical Care in Diabetes (2023)**[25]	Hypertension/blood pressure control • Blood pressure should be measured at every routine visit. When possible, patients found to have elevated blood pressure (systolic blood pressure 120 to 129 mmHg and diastolic <80 mmHg) should have blood pressure confirmed using multiple readings, including measurements on a separate day, to diagnose hypertension. Patients with blood pressure ≥180/110 and cardiovascular disease could be diagnosed with hypertension at a single visit. • All hypertensive patients with diabetes should monitor their blood pressure at home. • For patients with diabetes and hypertension, blood pressure targets should be individualized through a shared decision-making process that addresses cardiovascular risk, potential adverse effects of antihypertensive medications, and patient preferences. • Individuals with diabetes and hypertension qualify for antihypertensive drug therapy when the blood pressure is persistently elevated ≥130/80 mmHg. The on-treatment target blood pressure goal is <130/80 mmHg, if it can be safely

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	attained. • In pregnant patients with diabetes and preexisting hypertension, a blood pressure target of 110 to 135/85 is suggested in the interest of reducing the risk for accelerated maternal hypertension and minimizing impaired fetal growth. • For patients with blood pressure >120/80, lifestyle intervention consists of weight loss when indicated, a Dietary Approaches to Stop Hypertension (DASH)-style eating pattern including reducing sodium and increasing potassium intake, moderation of alcohol intake, and increased physical activity. • Patients with confirmed office-based blood pressure ≥130/80 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of pharmacologic therapy to achieve blood pressure goals. • Patients with confirmed office-based blood pressure ≥160/100 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of two drugs or a single pill combination of drugs demonstrated to reduce cardiovascular events in patients with diabetes. • Treatment for hypertension should include drug classes demonstrated to reduce cardiovascular events in patients with diabetes (ACE inhibitors, angiotensin receptor blockers, thiazide-like diuretics, or dihydropyridine calcium channel blockers). ACE inhibitors or angiotensin receptor blockers are recommended first-line therapy for hypertension in people with diabetes and coronary artery disease. • Multiple-drug therapy is generally required to achieve blood pressure targets (but not a combination of ACE inhibitors and angiotensin receptor blockers). • An ACE inhibitor or angiotensin receptor blocker, at the maximum tolerated dose indicated for blood pressure treatment, is the recommended first-line treatment for hypertension in patients with diabetes and urinary albumin–to–creatinine ratio ≥300 mg/g creatinine or 30 to 299 mg/g creatinine. If one class is not tolerated, the other should be substituted. • For patients treated with an ACE inhibitor, angiotensin receptor blocker, or diuretic, serum creatinine/estimated glomerular filtration rate and serum potassium levels should be monitored at least annually. • Patients with hypertension who are not meeting blood pressure targets on three classes of antihypertensive medications (including a diuretic) should be considered for mineralocorticoid receptor antagonist therapy. <u>Chronic kidney disease</u> • At least once a year, assess urinary albumin (e.g., spot urinary albumin–to–creatinine ratio) and estimated glomerular filtration rate in patients with type 1 diabetes with duration of five or more years and in all patients with type 2 diabetes. • In people with established diabetic kidney disease, urinary albumin (e.g., spot urinary albumin-to-creatinine ratio) and estimated glomerular filtration rate should be monitored one to four times per year depending on the stage of the disease. Optimize glucose control to reduce the risk or slow the progression of chronic kidney disease (CKD). • For patients with type 2 diabetes and diabetic kidney disease, use of a sodium-glucose cotransporter 2 inhibitor in patients with an estimated glomerular filtration rate ≥20 mL/min/1.73 m^2 and urinary albumin ≥200 mg/g creatinine is recommended to reduce CKD progression and cardiovascular events. • For patients with type 2 diabetes and diabetic kidney disease, use of a sodium–glucose cotransporter 2 inhibitor is recommended to reduce chronic kidney disease progression and cardiovascular events in patients with an estimated glomerular filtration rate ≥20 mL/min/1.73 m^2 and urinary albumin ranging from normal to 200 mg/g creatinine. • In people with type 2 diabetes and diabetic kidney disease, consider use of

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	sodium–glucose cotransporter 2 inhibitors (if estimated glomerular filtration rate is ≥20 mL/min/1.73 m^2), a glucagon-like peptide 1 agonist, or a nonsteroidal mineralocorticoid receptor antagonist (if estimated glomerular filtration rate is ≥25 mL/min/1.73 m^2) additionally for cardiovascular risk reduction. • In people with chronic kidney disease and albuminuria who are at increased risk for cardiovascular events or chronic kidney disease progression, a nonsteroidal mineralocorticoid receptor antagonist shown to be effective in clinical trials is recommended to reduce chronic kidney disease progression and cardiovascular events. • Optimize blood pressure control and reduce blood pressure variability to reduce the risk or slow the progression of CKD. • Do not discontinue renin-angiotensin system blockade for minor increases in serum creatinine (≤30%) in the absence of volume depletion. • For people with nondialysis-dependent stage 3 or higher CKD, dietary protein intake should be a maximum of 0.8 g/kg body weight per day (the recommended daily allowance). For patients on dialysis, higher levels of dietary protein intake should be considered, since protein energy wasting is a major problem in some dialysis patients. • In nonpregnant patients with diabetes and hypertension, either an ACE inhibitor or an angiotensin receptor blocker is recommended for those with modestly elevated urinary albumin–to–creatinine ratio (30 to 299 mg/g creatinine) and is strongly recommended for those with urinary albumin–to–creatinine ratio ≥300 mg/g creatinine and/or estimated glomerular filtration rate <60 mL/min/1.73 m^2. • Periodically monitor serum creatinine and potassium levels for the development of increased creatinine and hyperkalemia when ACE inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists are used, or hypokalemia when diuretics are used. • An ACE inhibitor or an angiotensin receptor blocker is not recommended for the primary prevention of CKD in patients with diabetes who have normal blood pressure, normal urinary albumin–to–creatinine ratio (<30 mg/g creatinine), and normal estimated glomerular filtration rate. • Patients should be referred for evaluation by a nephrologist if they have continuously increasing urinary albumin levels and/or continuously decreasing estimated glomerular filtration rate and an estimated glomerular filtration rate <30 mL/min/1.73 m^2. • Promptly refer to a nephrologist for uncertainty about the etiology of kidney disease, difficult management issues, and rapidly progressing kidney disease.
American Urological Association: **Management of Benign Prostatic Hyperplasia/ Lower Urinary Tract Symptoms (2021)**[8]	<u>Medical therapy</u> • Offer one of the following α-blockers as a treatment option for patients with bothersome, moderate to severe lower urinary tract symptoms/benign prostatic hyperplasia (LUTS/BPH): alfuzosin, doxazosin, silodosin, tamsulosin, or terazosin. • When prescribing an α-blocker for the treatment of LUTS/BPH, the choice of α-blocker should be based on patient age and comorbidities, and different adverse event profiles (e.g., ejaculatory dysfunction, changes in blood pressure). • When initiating α-blocker therapy, patients with planned cataract surgery should be informed of the associated risks and be advised to discuss these risks with their ophthalmologists. • For the purpose of symptom improvement, 5α-reductase inhibitor (5-ARI) monotherapy should be used as a treatment option in patients with LUTS/BPH with prostatic enlargement as judged by a prostate volume of > 30cc on imaging, a prostate specific antigen (PSA) > 1.5ng/dL, or palpable prostate enlargement on digital rectal exam (DRE).

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	• 5-ARIs alone or in combination with α-blockers are recommended as a treatment option to prevent progression of LUTS/BPH and/or reduce the risks of urinary retention and need for future prostate-related surgery. • Before starting a 5-ARI, clinicians should inform patients of the risks of sexual side effects, certain uncommon physical side effects, and the low risk of prostate cancer. • Clinicians may consider 5-ARIs as a treatment option to reduce intraoperative bleeding and peri- or postoperative need for blood transfusion after transurethral resection of the prostate (TURP) or other surgical intervention for BPH. • For patients with LUTS/BPH irrespective of comorbid erectile dysfunction (ED), 5mg daily tadalafil should be discussed as a treatment option. • 5-ARI in combination with an α-blocker should be offered as a treatment option only to patients with LUTS associated with demonstrable prostatic enlargement as judged by a prostate volume of > 30cc on imaging, a PSA >1.5ng/dL, or palpable prostate enlargement on DRE. • Anticholinergic agents, alone or in combination with an α-blocker, may be offered as a treatment option to patients with moderate to severe predominant storage LUTS. • β-3-agonists in combination with an α-blocker may be offered as a treatment option to patients with moderate to severe predominate storage LUTS. • Clinicians should not offer the combination of low-dose daily 5mg tadalafil with α-blockers for the treatment of LUTS/BPH as it offers no advantages in symptom improvement over either agent alone. • Physicians should prescribe an oral α-blocker prior to a voiding trial to treat patients with acute urinary retention (AUR) related to BPH. • Patients newly treated for AUR with α-blockers should complete at least three days of medical therapy prior to attempting trial without a catheter (TWOC). Clinicians should inform patients who pass a successful TWOC for AUR from BPH that they remain at increased risk for recurrent urinary retention.
European Association of Urology: **Non-neurogenic Male LUTS (2023)**[9]	Pharmacological treatment • Offer α1-blockers to men with moderate-to-severe lower urinary tract symptoms (LUTS). • α1-blockers are effective in reducing urinary symptoms (IPSS) and increasing the peak urinary flow rate (Q_{max}) compared with placebo. • Alfuzosin, terazosin and doxazosin showed a statistically significant increased risk of developing vascular-related events compared with placebo. • Alfuzosin, doxazosin, tamsulosin or terazosin exposure has been associated with an increased risk of intra-operative floppy iris syndrome (IFIS). • Ejaculatory dysfunction is significantly more common with α1-blockers than with placebo, particularly with more selective α1-blockers such as tamsulosin and silodosin. • Use 5α-reductase inhibitors in men who have moderate-to-severe LUTS and an increased risk of disease progression (e.g., prostate volume > 40 mL). • Counsel patients about the slow onset of action of 5α-reductase inhibitors. • Use muscarinic receptor antagonists in men with moderate-to-severe LUTS who mainly have bladder storage symptoms. • Do not use antimuscarinic overactive bladder medications in men with a post-void residual volume > 150 mL. • Use β-3 agonists in men with moderate-to-severe LUTS who mainly have bladder storage symptoms. • Use phosphodiesterase type 5 inhibitors in men with moderate-to-severe LUTS with or without erectile dysfunction. • Offer combination treatment with an α1-blocker and a 5α-reductase inhibitor to men with moderate-to-severe LUTS and an increased risk of disease

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	progression (e.g., prostate volume > 40 mL). • Offer combination treatment with an α1-blocker and a 5α-reductase inhibitor to men with moderate-to-severe LUTS and an increased risk of disease progression (e.g. prostate volume > 40 mL). • Use combination treatment of a α1-blocker with a muscarinic receptor antagonist in patients with moderate-to-severe LUTS if relief of storage symptoms has been insufficient with monotherapy with either drug. Do not prescribe combination treatment in men with a post-void residual volume > 150 mL. • Use combination treatment of a α1-blocker with mirabegron in patients with persistent storage LUTS after treatment with α1-blocker monotherapy.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the α-adrenergic blocking agents are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Alpha-Adrenergic Blocking Agents[3-6]

Indication	Doxazosin	Prazosin	Terazosin
Benign Prostatic Hyperplasia			
Treatment of signs and symptoms of benign prostatic hyperplasia	✔		
Treatment of symptomatic benign prostatic hyperplasia			✔
Hypertension			
Treatment of hypertension	✔ * (immediate-release)	✔ *	✔ *

*Alone or in combination with other antihypertensive agents.

IV. Pharmacokinetics

The pharmacokinetic parameters of the α-adrenergic blocking agents are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Alpha-Adrenergic Blocking Agents[2]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Doxazosin	IR: 65 ER: 54 to 59	98	Liver, extensive (% not reported)	Renal (9) Feces (63)	IR: 22 ER: 15 to 19
Prazosin	56 to 63	92 to 97	Liver, extensive (% not reported)	Renal (<1) Feces, extensive (% not reported)	2 to 3
Terazosin	90	90 to 94	Liver, extensive (% not reported)	Renal (40) Feces (55 to 60)	9 to 12

ER=extended-release, IR=immediate-release

V. Drug Interactions

Major drug interactions with the α-adrenergic blocking agents are listed in Table 5.

Table 5. Major Drug Interactions with the Alpha-Adrenergic Blocking Agents[2]

Generic Name(s)	Interaction	Mechanism
Alpha-adrenergic blocking agents (doxazosin, prazosin, terazosin)	Asenapine	Concurrent use of asenapine and alpha-adrenergic antagonists may result in additive hypotensive effect.
Alpha-adrenergic blocking agents (doxazosin, prazosin, terazosin)	Phosphodiesterase type 5 Inhibitors	Hypotension may occur when alpha-blockers and phosphodiesterase type 5 inhibitors are co-administered. Alpha-blockers and phosphodiesterase type 5 inhibitors may exert additive pharmacologic activity.
Alpha-adrenergic blocking agents (doxazosin)	Boceprevir	Concurrent use of boceprevir and doxazosin may result in increased doxazosin exposure.

VI. Adverse Drug Events

The most common adverse drug events reported with the α-adrenergic blocking agents are listed in Table 6. These agents can cause marked hypotension and syncope with sudden loss of consciousness with the first few doses. This "first-dose" effect can be minimized by administration of the first dose at bedtime. Hypotension and syncope can also occur with dose increases, addition of other antihypertensives, and therapy interruptions. The elderly are more at risk for this adverse reaction.

Table 6. Adverse Drug Events (%) Reported with the Alpha-Adrenergic Blocking Agents[1-6]

Adverse Events	Doxazosin	Prazosin	Terazosin
Cardiovascular			
Angina	<1	✔	-
Arrhythmia	1	-	<1
Atrial fibrillation	-	-	<1
Bradycardia	<1	✔	-
Chest pain	1 to 2	-	<1
Edema	3 to 4	1 to 4	-
Flushing	1	✔	-
Hypotension	1 to 2	✔	-
Myocardial infarction	<1	-	-
Orthostatic hypotension	<2	1 to 4	1 to 4
Palpitations	1 to 2	5	≤4
Peripheral edema	-	-	1 to 6
Peripheral ischemia	<1	-	-
Syncope	1 to 2	1 to 4	≤1
Tachycardia	<1	<1	≤2
Vasodilation	-	-	<1
Central Nervous System			
Abnormal thinking	<1	-	-
Agitation	<1	-	-
Amnesia	<1	-	-
Anxiety	1	-	<1
Ataxia	1	-	-
Cerebrovascular accident	<1	-	-
Confusion	<1	-	-
Decreased energy	-	7	-
Depersonalization	<1	-	-
Depression	1	1 to 4	-
Dizziness	5 to 19	10	9 to 19
Drowsiness	-	8	-
Emotional lability	<1	-	-

Adverse Events	Doxazosin	Prazosin	Terazosin
Fatigue	8 to 12	-	-
Fever	<1	-	<1
Hallucinations	-	<1	-
Headache	5 to 14	8	1 to 16
Hypertonia	1	-	-
Insomnia	1	✔	<1
Kinetic disorders	1	-	-
Migraine	<1	-	-
Nervousness	2	1 to 4	-
Paranoia	<1	-	-
Paresis	<1	-	-
Paresthesia	≤1	<1	≤3
Somnolence	1 to 5	-	4 to 5
Stroke	<1	-	-
Vertigo	2 to 4	1 to 4	1
Dermatological			
Alopecia	-	<1	-
Lichen planus	-	<1	-
Pallor	<1	-	-
Rash	1	1 to 4	<1
Pruritus	1	<1	<1
Urticaria	<1	<1	-
Endocrine and Metabolic			
Breast pain	<1	-	-
Gout	<1	-	<1
Gynecomastia	<1	✔	-
Pancreatitis	-	<1	-
Gastrointestinal			
Abdominal pain	2	<1	<1
Anorexia	<1	-	-
Appetite decreased	<1	-	-
Cholestasis	<1	-	-
Constipation	1	1 to 4	<1
Diarrhea	2	1 to 4	<1
Dyspepsia	1 to 2	-	<1
Fecal incontinence	<1	-	-
Flatulence	1	-	<1
Gastroenteritis	<1	-	-
Nausea	1 to 3	5	2 to 4
Vomiting	<1	1 to 4	<1
Xerostomia	2	1 to 4	<1
Genitourinary			
Hematuria	<1	-	-
Impotence	1	<1	≤2
Libido decreased	-	-	<1
Micturition abnormality	<1	-	-
Nocturia	<1	-	-
Polyuria	2	-	<1
Priapism	<1	<1	<1
Renal calculus	<1	-	-
Sexual dysfunction	2	-	-
Urinary frequency	-	1 to 4	-
Urinary incontinence	1	<1	<1
Urinary tract infection	1	-	<1

Adverse Events	Doxazosin	Prazosin	Terazosin
Hematologic			
Leukopenia	<1	-	-
Neutropenia	<1	-	-
Purpura	<1	-	-
Thrombocytopenia	<1	-	<1
Hepatic			
Jaundice	<1	-	-
Liver function tests increased	<1	<1	-
Laboratory Test Abnormalities			
Hypokalemia	<1	-	-
Musculoskeletal			
Arthralgia	1	✔	<1
Arthritis	1	-	<1
Back pain	2 to 3	-	≤2
Extremity pain	-	-	<1
Joint disorder	-	-	<1
Muscle cramps	1	-	-
Muscle weakness	1	-	7 to 11
Myalgia	1	-	<1
Neck pain	-	-	<1
Pain	2	✔	-
Shoulder pain	-	-	<1
Weakness	<1	7	-
Respiratory			
Bronchitis	-	-	<1
Bronchospasm	<1	-	-
Cough	-	-	<1
Dyspnea	1 to 3	1 to 4	2 to 3
Epistaxis	1	1 to 4	<1
Hepatitis	<1	-	-
Nasal congestion	-	1 to 4	2 to 6
Pharyngitis	-	-	<1
Respiratory disorder	1	-	-
Respiratory tract infection	5	-	-
Rhinitis	3	-	<1
Sinusitis	-	-	≤3
Special Senses			
Abnormal vision	1 to 2	-	<1
Blurred vision	-	1 to 4	≤2
Cataracts	-	<1	-
Conjunctivitis	1	-	<1
Hypoesthesia	<1	-	-
Intraoperative floppy iris syndrome	<1	<1	<1
Pigmentary mottling and serous retinopathy	-	<1	-
Sclera reddened	-	1 to 4	-
Tinnitus	1	<1	<1
Parosmia	<1	-	-
Other			
Allergic reaction	<1	✔	<1
Anaphylaxis	-	-	<1
Diaphoresis	1	✔	<1
Facial edema	1	-	<1
Infection	<1	-	-
Influenza-like symptoms	1	-	≤2

Adverse Events	Doxazosin	Prazosin	Terazosin
Lymphadenopathy	<1	-	-
Rigors	<1	-	-
Vasculitis	-	✔	-

✔ Percent not specified
- Event not reported

VII. Dosing and Administration

The usual dosing regimens for the α-adrenergic blocking agents are listed in Table 7. Treatment should be initiated at bedtime and at the lowest dose to minimize the likelihood of the "first-dose" effect. Dosages should be titrated up slowly to achieve the desired response. If therapy is interrupted for more than a few days, the initial dosing regimen and titration schedule should be reinstituted. Other antihypertensive agents should be added cautiously to reduce the risk of developing significant hypotension.[1-6]

Table 7. Usual Dosing Regimens for the Alpha-Adrenergic Blocking Agents[1-6]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Doxazosin	Benign prostatic hyperplasia: Extended-release: initial, 4 mg once daily; maintenance, 4 to 8 mg daily; maximum, 8 mg/day Tablet: initial, 1 mg once daily; maintenance, 1 to 8 mg once daily; maximum:, 8 mg/day Hypertension: Tablet: initial, 1 mg once daily; maintenance, 1 to 16 mg once daily; maximum, 16 mg/day	Safety and efficacy in children have not been established.	Extended-release tablet: 4 mg 8 mg Tablet: 1 mg 2 mg 4 mg 8 mg
Prazosin	Hypertension: Capsule: initial, 1 mg two to three times a day; maintenance, 6 to 15 mg/day in divided doses; maximum, 40 mg/day	Safety and efficacy in children have not been established.	Capsule: 1 mg 2 mg 5 mg
Terazosin	Benign prostatic hyperplasia: Capsule: initial, 1 mg at bedtime; maintenance, 1 to 10 mg/day; maximum, 20 mg/day Hypertension: Capsule: initial, 1 mg at bedtime; maintenance, 1 to 20 mg once daily; maximum, 20 mg/day	Safety and efficacy in children have not been established.	Capsule: 1 mg 2 mg 5 mg 10 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the α-adrenergic blocking agents are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Alpha-Adrenergic Blocking Agents

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Benign Prostatic Hyperplasia				
Lee et al.[26] (2011) α-adrenergic blocking agent vs no α-adrenergic blocking agent All patients were receiving finasteride. Patients were divided into 2 groups based on treatment pattern (α-adrenergic blocking agent monotherapy vs α-adrenergic blocking agent combined with finasteride) and further divided into 4 subgroups based on severity of storage symptoms (IPSS	MC, RETRO Patients ≥50 years of age with LUTS consistent with moderate to severe BPH	N=1315 4 years	Primary: Prostate volume, PSA, IPSS, Q_{max} Secondary: Not reported	Primary: All groups showed significant improvements in IPSS total scores, IPSS voiding subscores and QOL at one year (P values not reported). Total IPSS from baseline to year four decreased by -11.5 in group IV compared to -0.18 in group I (P<0.001), -6.1 in group II (P=0.97) and -2.6 in group III (P=0.031). However, IPSS storage subscores only improved in patients with high (≥6) storage subscores at baseline (P value not reported). After one year, prostate volume and PSA were reduced by 21.3 and 47.0%, respectively, in the combination groups compared to an increase of 9 and 18%, respectively, in the monotherapy groups (P<0.001 for both). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
storage domain score ≥6 vs <6). Group I was classified as monotherapy and storage scores <6, group II as monotherapy and storage scores ≥6, group III as combination therapy and storage scores <6 and group IV as combination therapy and storage scores ≥6.				
Demir et al.[27] (2009) Doxazosin 4 mg QD Patients were grouped into 2 groups according to self-reported erectile status: patients who reported the presence of erectile dysfunction (group I) and patients who reported the absence of erectile dysfunction (group	RETRO Males >40 years of age who had been in a steady sexual relationship for the past 6 months and were admitted to urology clinics with complaints of BPH	N=64 6 weeks	Primary: Not reported Secondary: Not reported	Primary Endpoints: Not reported Secondary Endpoints: Not reported Mean reductions in total IPSS and quality of life compared to baseline were -7.7±6.1 and 1.5±1.5 (P=0.006 and P=0.024, respectively). Treatment with doxazosin also resulted in significant improvements in Q_{max} over baseline (3.2±4.6 mL/s; P=0.002). Both groups exhibited significant improvements in IPSS and quality of life scores over baseline (P<0.001 for both). Improvements in LUTS appeared to be numerically greater in group II; however, quality of life was the only parameter for which a significant improvement was seen compared to group I (-1.0±1.8 vs -1.9±1.1, for groups I and II respectively; P=0.018). Mean International Index of Erectile Function erectile function domain scores increased in group I and slightly decreased in group II when compared to baseline. Mean changed of other International Index of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
II)				Erectile Function domains were not significant in either group. When stratified according to erectile dysfunction severity, the mean changes in International Index of Erectile Function erectile function domain scores over baseline were: 4.3±6.0, 0.3±5.3, -1.2±1.6 in those participants with severe, moderate, and mild erectile dysfunction, respectively. No serious adverse events were observed during the treatment course in either group.
Sun et al.[28] (abstract) (2010) Doxazosin SR 4 mg QD At week 4, subjects who achieved an increase in Q_{max} ≥3 mL/s and a ≥30% reduction in the total IPSS continued on doxazosin SR 4 mg for the remaining 4 weeks; all other subjects were titrated up to 8 mg QD.	OL, PM Taiwanese males with BPH	N=80 8 weeks	Primary: Change from baseline Q_{max} and IPSS Secondary: Safety	Primary Endpoints: Baseline Q_{max} and IPSS were 10.7+3.4 mL/s and 20.6+5.4, respectively. At week eight, a significant increase from baseline in Q_{max} of 3.3+4.6 mL/s (95% CI, 2.2 to 4.4, P<0.001) and a significant decrease in total IPSS of -8.9+7.0 (95% CI, -10.5 to -7.3; P<0.001) was observed. Secondary Endpoints: The most common treatment-related adverse event was dizziness.
Kirby et al.[29] (2001) Doxazosin vs	2 DB, MC, PG, RCT Men 50 to 80 years of age with BPH	N=1,475 17 weeks	Primary: Change from baseline in IPSS and Qmax Secondary: Sexual function,	Primary: A 45% significant decrease from baseline in IPSS was attained with both formulations of doxazosin compared to a 34% decrease with placebo after 13 weeks (P<0.001 vs placebo). Doxazosin SR was as effective as doxazosin in improving IPSS with a least squares mean difference of 0.07 (SEM, 0.28; 95% CI, -0.47 to 0.61; P=0.799).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
doxazosin SR vs placebo Comparison with placebo was evaluated in 1 of the 2 trials.			tolerability	Effect on Qmax was also comparable between the two doxazosin formulations; a least square mean difference of 0.19 (SEM, 0.23; 95% CI, -0.27 to 0.64; P=0.426) was reported. The improvements were significantly greater compared to placebo (P<0.001 for both). Secondary: Only the non-PC trial evaluated sexual function. Both formulations of doxazosin demonstrated modest but significant improvements in sexual function from baseline as measured by the IIEF (P≤0.001 for doxazosin SR and P<0.05 for doxazosin). Forty one percent of patients receiving doxazosin SR, 54% of patients receiving doxazosin and 39% of patients receiving placebo experienced adverse events (P<0.001 for differences among treatments). Headache, dizziness, respiratory tract infections and asthenia were the most frequently reported side effects of active treatment.
Keten et al.[30] (2015) Doxazosin XL 4 mg (group 1) vs doxazosin XL 8 mg (group 2) Patients with an inadequate response to 4 mg treatment were switched to 8 mg after one month (group 1b)	PRO Patients aged >45 years, with a total PSA <4 ng/mL, IPSS of >7, and Q_{max} ≤15 mL/s	N=162 4 months	Primary: IPSS, Q_{max}, quality of life (QoL) score Secondary: Not reported	Primary: From the time of presentation to the first month follow-up, the IPSS and QoL values had decreased more in group 2 compared with group 1 (P_{IPSS}=0.028, P_{Qmax}=0.206, P_{QoL}=0.038, and P_{PVR}=0.070). The comparison of the patients in Group 1b who used 4 and 8 mg doxazosin XL for one month showed that during the use of 4 mg doxazosin XL, the change in the IPSS was 1.3 ± 1.3 units, and during the use of 8 mg doxazosin XL, the change was 3.6 ± 2.5 units (P<0.001). The change in the Q_{max} values for 4 and 8 mg doxazosin XL was found to be 1.6 ± 1.8 and 3.2 ± 2.7 mL/s, respectively (P=0.019). For the 4 mg doxazosin XL, the QoL values increased by 0.4 ± 0.6 units, and during the use of 8 mg doxazosin XL, the QoL values decreased by 1.8 ± 0.7 units (P<0.001). No difference was found concerning the adverse reactions between the groups (P>0.05). Secondary: Not reported
Samli et al.[31]	RCT, XO	N=50	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2004) Doxazosin 8 mg QD vs terazosin 10 mg QD	Men with LUTS associated with BPH	3 months	Change from baseline in IPSS and Qmax Secondary: Not reported	The proportion of patients who showed improvement in both IPSS and Qmax were 44 and 40% of patients receiving doxazosin and Terazosin, respectively. After three months, both treatments resulted in a significantly increased Qmax (P<0.001) and a significantly decreased IPSS (P<0.01). The number of patients who did not show improvement and had to switch to the other treatment was 19. Of these patients, two showed improvement in both IPSS and Qmax, two showed improvement in IPSS only and 15 did not show any improvement. Secondary: Not reported
Kaplan et al.[32] (1997) Doxazosin 4 to 8 mg QD vs terazosin 5 to 10 mg QD	OL, PRO Men >80 years of age with BPH	N=36 6 months	Primary: Change from baseline in Qmax and AUA SS Secondary: Not reported	Primary: There was significant improvement in Qmax (P<0.008) and AUA SS (P<0.01) with both treatments. There were small, nonsignificant decreases in blood pressure with both treatments. Secondary: Not reported
Kaplan et al.[33] (1995) Doxazosin 4 mg QD in the morning vs doxazosin 4 mg QD in the evening vs terazosin 5 mg QD in the morning	RCT Men without HTN and symptomatic prostatism	N=43 4 to 17 months	Primary: Changes from baseline in Boyarsky symptom score, Qmax and blood pressure; adverse events Secondary: Not reported	Primary: There were significant improvements in Boyarsky symptom scores and Qmax with all four treatments (P<0.05), with no significant differences between the treatments (P values not reported). Adverse events were significantly decreased with evening doses (P<0.05). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs terazosin 5 mg QD in the evening				
Bozlu et al.[34] (2004) Doxazosin 4 mg QD vs terazosin 5 mg QD vs alfuzosin 2.5 mg TID vs tamsulosin 0.4 mg QD	RETRO Patients with LUTS suggestive of BPH with and without diabetes	N=281 6 months	Primary: Change from baseline in IPSS, bother score, Qmax and PVR Secondary: Not reported	Primary: Doxazosin, terazosin and alfuzosin significantly improved IPSS, bother scores, Qmax and PVR compared to baseline (P<0.001). IPSS and bother scores were significantly improved in diabetic patients compared to nondiabetic patients (P<0.01). There was no significant differences among the treatments in the improvement rates of any of the parameters (P>0.05). Secondary: Not reported
Xue et al.[35] (2007) Doxazosin SR 4 mg QD vs tamsulosin 0.2 mg QD	RCT Chinese men with confirmed BPH	N=117 8 weeks	Primary: Efficacy, safety Secondary: Not reported	Primary: Both treatments significantly improved the IPSS (total, irritative subscore, and obstructive subscore; P=0.001 for all) and Qmax (P=0.001). Other differences between groups were not statistically significant. Secondary: Not reported
Rahardjo et al.[36] (2006)	MC, OL, RCT Patients with LUTS	N=101 6 weeks	Primary: Changes from baseline in IPSS,	Primary: The total IPSS decreased significantly with both tamsulosin and doxazosin compared to baseline (P<0.001), with tamsulosin being associated with a

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Doxazosin 2 mg QD vs tamsulosin 0.2 mg QD	due to BPH		Qmax, average urinary flow rate and residual urine; safety Secondary: Not reported	significant decrease compared to doxazosin (P=0.036). Qmax, average urinary flow rate and residual urine significantly improved with tamsulosin only (P<0.001, P<0.001, and P<0.05, respectively). There were no significant differences in SBP or DBP with tamsulosin; however, doxazosin resulted in significant differences in SBP (P<0.01) but not in DBP (P value not reported) at the end of the study. Tamsulosin was well tolerated; only three patients (six percent) receiving tamsulosin reported an adverse event (dizziness), while 11 patients (22%) with doxazosin reported an adverse event (dizziness), one of whom withdrew from the trial. Secondary: Not reported
Pompeo et al.[37] (2006) Doxazosin SR 4 mg QID vs tamsulosin 0.4 mg QID	DB, DD, RCT Brazilian patients with BPH	N=165 12 week	Primary: Absolute and percentage change from baseline in symptoms measured by IPSS Secondary: Quality of life question from the IPSS and questions six and seven of the SFAQ	Primary: Doxazosin and tamsulosin improved IPSS with no significant differences between the two after 12 weeks. During weeks four to eight, tamsulosin demonstrated a slower improvement (P<0.001) in IPSS compared to doxazosin. Secondary: The proportion of satisfied patients did not change over the course of the trial with doxazosin, while it did change significantly between weeks four and eight with tamsulosin (P=0.006); suggesting that a change for the better was observed earlier with doxazosin. After 12 weeks, the proportion of patients with little or no difficulty at ejaculation (question six of SFAQ) was significantly higher with doxazosin (P=0.019). Both treatments were well tolerated.
Cao et al.[38] (2016) Doxazosin SR 4 mg QD vs	OL, PRO, RCT Men 50 to 80 years of age with newly diagnosed symptoms of BPH	N=192 12 weeks	Primary: IPSS Secondary: Quality of life and Qmax	Primary: After six weeks of treatment, LUTS were improved in both groups, as seen by the change in IPSS from baseline. There was no significant difference between groups in terms of total IPSS (P=0.86). At 12 weeks, greater improvement of total IPSS was observed in the doxazosin group than in the tamsulosin group (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
tamsulosin 0.2 mg QD Both groups received tolterodine ER 4 mg QD				Secondary: After six weeks treatment there was no significant difference between the groups in Qmax (P=0.19). However, quality of life was significantly improved in the doxazosin group compared to the tamsulosin group (P=0.01). At 12 weeks Qmax showed greater improvement in the doxazosin group (14.1±1.6 mL/s) than in the tamsulosin group (13.5±2.1 mL/s; P=0.03). In addition, quality of life (2.5±0.67 vs 3.1±0.7; P<0.001) of the doxazosin group was more improved (lower score represents better quality of life).
Johnson et al.[39] (2007) Doxazosin 2, 4, or 8 mg QD vs finasteride 5 mg QD vs doxazosin 2, 4, or 8 mg QD plus finasteride 5 mg QD vs placebo	PC, RCT Men with LUTS suggestive of BPH	N=3,047 4 years	Primary: Efficacy (mean reduction in self-reported nightly nocturia at 1 and 4 years) Secondary: Not reported	Primary: The number of men reporting one or more episodes of nocturia who finished ≥12 months of the trial came to a total of 2,583. Mean nocturia was similar with all treatments at baseline. Mean nocturia was reduced after one year by 0.35, 0.40, 0.54 and 0.58 with placebo, finasteride, doxazosin and combination therapy, respectively. Reductions with doxazosin and combination therapy were significantly greater compared to placebo (P<0.05). After four years, nocturia was also significantly reduced in patients receiving doxazosin and combination therapy (P<0.05 vs placebo). In men >70 years of age (n=495) all treatments significantly reduced nocturia after one year (Finasteride, 0.29; Doxazosin, 0.46 and combination therapy, 0.42) compared to placebo (0.11; P<0.05 for all). Secondary: Not reported
Crawford et al.[40] (2006) Doxazosin 4 to 8 mg QD vs	PC, RCT Men with LUTS suggestive of BPH	N=737 4 years	Primary: Time to overall clinical progression of BPH (either a confirmed ≥4 point increase in AUA	Primary: The rate of overall clinical progression of BPH events with placebo was 4.5 per 100 person-years, for a cumulative incidence (among men who had at least four years of follow up data) of 17%. The risk of BPH progression was significantly greater with placebo with a baseline TPV ≥31 mL compared to a baseline TPV <31 mL (P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
finasteride 5 mg QD vs doxazosin 4 to 8 mg QD plus finasteride 5 mg QD vs placebo			SS, acute urinary retention, incontinence, renal insufficiency or recurrent urinary tract infection) Secondary: Not reported	The risk of BPH progression was significantly greater with placebo with a baseline PSA ≥1.6 ng/dL compared to a baseline PSA <1.6 ng/dL (P=0.0009). The risk of BPH progression was significantly greater with placebo with a baseline Qmax <10.6 mL/second compared to a baseline Qmax ≥10.6 mL/second (P=0.011) The risk of BPH progression was significantly greater with placebo with a baseline PVR ≥39 mL compared to a baseline PVR <39 mL (P=0.0008). The risk of BPH progression was significantly greater with placebo with baseline age ≥62 years compared to those aged <62 years (P=0.0002). Secondary: Not reported
Kaplan et al.[41] (2006) Doxazosin 4 to 8 mg QD vs finasteride 5 mg QD vs doxazosin 4 to 8 mg QD plus finasteride 5 mg QD vs	PC, RCT Men with LUTS suggestive of BPH	N=3,047 4 years	Primary: Overall clinical progression of BPH (either a confirmed ≥4 point increase in AUA SS, acute urinary retention, incontinence, renal insufficiency or recurrent urinary tract infection) Secondary: Need for invasive therapy for BPH, change from baseline in AUA SS and Qmax	Primary: In patients with a small prostate (baseline TPV >25 mL) combination therapy was no better than doxazosin for decreasing the risk of clinical progression of BPH and need for invasive therapy as well as improving AUA SS and Qmax. However, in patients with a moderate sized (25 to >40 mL) or enlarged (≥40 mL) gland, combination therapy led to a clinical benefit in these outcomes that was "superior" to that of doxazosin or finasteride (P<0.05). Secondary: In men with baseline TPV <25 mL, there was no difference in the risk of invasive therapy for combination therapy relative to doxazosin or finasteride. However, in the baseline TPV subgroups of 25 to <40 and ≥40 mL there was a significant and marked percent risk decrease in invasive therapy, of around 60 to 80%, for combination therapy compared to doxazosin (P<0.05). In men with baseline TPV <25 mL, the improvement after four years in AUA SS for combination therapy relative to doxazosin was not different, whereas the improvement for combination therapy compared to finasteride

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				was significantly different in favor of combination therapy (P<0.05). In the baseline TPV subgroups of 25 to <40 and ≥40 mL, the improvement in AUA SS with combination therapy was significantly better than that for doxazosin and finasteride (P<0.05).
Kaplan et al.[42] (2008) Doxazosin 4 to 8 mg/day vs finasteride 5 mg/day vs doxazosin 4 to 8 mg/day and finasteride 5 mg/day vs placebo	DB, PC, RCT Men ≥50 years of age with an AUA SS of 8 to 30 and a Qmax of 4 to 15 ml/second with a voided volume of ≥125 mL	N=3,047 Mean 4.5 years	Primary: TPV Secondary: Not reported	Primary: Long-term treatment with finasteride alone or in combination with doxazosin led to a consistent reduction in TPV of approximately 25% compared to placebo in men with a relatively small prostate (baseline TPV less than 25 mL and 25 to 30 mL) as well as those with a moderate size (greater than 30 to less than 40 mL) or enlarged prostate (40 mL or greater). Secondary: Not reported
Kirby et al.[43] (2003) PREDICT Doxazosin 1 to 8 mg QD vs finasteride 5 mg QD	DB, MC, PC, PRO, RCT Men 50 to 80 years of age with BPH and an enlarged prostate	N=1,095 52 weeks	Primary: Change from baseline in Qmax and IPSS Secondary: Tolerability	Primary: Doxazosin (3.6±0.3 mL/second) and combination therapy (3.8±0.3 mL/second) were associated with a significantly greater improvement in Qmax after one year compared to finasteride (1.8±0.3 mL/second; P≤0.0001) or placebo (1.4±0.3 mL/second; P≤0.0001). There were no differences between doxazosin and combination therapy or finasteride and placebo (P values not reported). Similar results were found with total IPSS. Again, doxazosin (3.6±0.3 mL/second) and combination therapy (3.8±0.3 mL/second) caused a significantly greater improvement in score over finasteride alone (1.8±0.3 mL/second; P<0.01) or placebo (1.4±0.3 mL/second; P≤0.0001). There

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs doxazosin 1 to 8 mg QD plus finasteride 5 mg QD vs placebo				were no differences between doxazosin and combination therapy or finasteride and placebo (P values not reported). Secondary: Doxazosin use increased the risk of asthenia, dizziness and hypotension, while impotence was reported most frequently with combination therapy.
Fwu et al.[44] (2013) MTOPS Doxazosin 4 or 8 mg QD vs finasteride 5 mg QD vs doxazosin 4 or 8 mg QD plus finasteride 5 mg QD vs placebo	DB, MC, RCT Patients ≥50 years of age with an AUA-SS of 8 to 30, a Qmax of 4 to 15 mL/second, and a minimum voided volume of 125 mL	N=2,872 4 years	Primary: Change in quality of life (QoL) using Benign Prostatic Hyperplasia Impact Index (BII), IPSS-QoL, and annually by the Outcomes Study Short-Form 36 (MOS-SF-36) Secondary: Not reported	Primary: Changes in the MOS-SF-36 scores from baseline to year four of follow-up by treatment group demonstrated a statistically significant reduction (worsening) for the subscales of physical functioning, role limitations due to physical problems, bodily pain, general health perception, and vitality in all treatment groups, except bodily pain in men assigned to finasteride. No significant change was observed in mental health in any treatment group. The subscale with the greatest reduction was role limitations due to physical problems. The decrease was greatest in the placebo group (−8.83, 95% CI, −12.09 to −5.58) and least in finasteride (−6.97, −10.19 to −3.74). The differences in changes for MOS-SF-36 subscales and summary scores between drug groups and placebo group were not statistically significant. Similarly, neither significant differences nor important effect sizes of the subscales and summary scores were observed when drug groups were compared with each other at year four. Compared with men assigned to placebo, men assigned to doxazosin and combination experienced a statistically significant improvement in the BII at year four. Men assigned to each of the drug groups also experienced a significant improvement in the IPSS-QoL compared with those assigned to placebo. Secondary: Not reported
Djavan et al.[45] (1999)	MA	N=6,333 (PC trials)	Primary: Changes from	Primary: There was no difference in efficacy among the four treatments. Alfuzosin

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Doxazosin vs terazosin vs alfuzosin vs tamsulosin	Men with LUTS suggestive of benign prostatic obstruction	N=507 (comparative trials)	baseline in total symptom score and maximum urinary flow rate, tolerability Secondary: Not reported	(IR 2.5 mg TID), alfuzosin (SR 5 mg BID), terazosin (5 to 10 mg/day), doxazosin (4 to 8 mg/day) and tamsulosin (0.4 mg/day) all produced comparable improvements in LUTS and Qmax (P values not reported). The total symptom score improved by 30 to 40% and the Qmax by 16 to 25%. Alfuzosin and tamsulosin were better tolerated than terazosin and doxazosin. Alfuzosin and tamsulosin had similar withdrawal rates as placebo. With terazosin and doxazosin, an additional 4 to 10% of patients withdrew from due to intolerability (P value not reported). Tamsulosin had less effect on blood pressure than alfuzosin (P value not reported). Tamsulosin also caused less symptomatic orthostatic hypotension than terazosin (P value not reported). Secondary: Not reported
Nickel et al.[46] (2008) Doxazosin 4 to 8 mg/day vs terazosin 1 to 10 mg/day vs alfuzosin 10 mg/day vs tamsulosin 0.4 mg/day	MA Men with BPH	26 trials 4 weeks to 4.5 years	Primary: Vascular-related adverse events with α1-adrenergic blockers including dizziness, hypotension, or syncope Secondary: Efficacy based on change from baseline of Qmax and change from baseline of AUA SI or IPSS	Primary: Treatment with α1-adrenergic blockers was associated with a significant increase in the development of a vascular-related adverse event compared to placebo (OR, 2.54; 95% CI, 2.00 to 3.23; P<0.0001). There was a higher risk of developing the primary composite end-point compared to placebo for alfuzosin (P=0.005), terazosin (P<0.0001), doxazosin (P<0.0001), and doxazosin SR (P<0.0001). Secondary: Alpha-1-adrenergic blockers improved Q_{max} by 1.32 mL/min compared to placebo (95% CI, 1.07 to 1.57; P<0.0001). The WMD in AUA SI/IPSS for all α1-adrenergic blockers was -1.92 points compared to placebo (95% CI, -2.71 to -1.14); P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				
MacDonald et al.[47] (2005) Doxazosin, tamsulosin, or finasteride vs alfuzosin vs alfuzosin plus finasteride or placebo	SR (11 trials) Men with symptomatic BPH	N=3,901 4 to 26 weeks	Primary: Change from baseline in IPSS Secondary: Change from baseline in Qmax and urinary symptom scores, adverse effects, incidence of treatment discontinuation	Primary: In the two trials comparing alfuzosin to other α-adrenergic blocking agents, doxazosin demonstrated the greatest improvement in IPSS (WMD, 1.70; 95% CI, 0.76 to 1.64; P=0.05). One trial evaluated alfuzosin vs finasteride or alfuzosin plus finasteride. Alfuzosin, both alone or in combination, significantly improved LUTS compared to finasteride. When compared to placebo, alfuzosin demonstrated a greater improvement in the IPSS with a WMD of -1.8 points (95% CI, -2.49 to -1.11). Secondary: No difference was found among α-adrenergic blocking agents in Qmax, while alfuzosin and tamsulosin (0.4 mg) demonstrated similar improvements in Boyarsky symptom scores. Alfuzosin, finasteride and combination treatment all had similar changes in Qmax; however, a subgroup analysis showed greater improvement in patients with obstruction with alfuzosin and combination therapy over finasteride. Qmax was 2.6 mL/second (10 to 54%) with alfuzosin vs 1.1 mL/second with placebo (2 to 29%). Alfuzosin demonstrated benefit over placebo in the mean urinary symptom score with a WMD of -0.90 point (95% CI, -0.94 to -0.87). The incidences of adverse events as well as withdrawal rates were comparable among α-adrenergic blocking agents. Vasodilatory effects were similar with alfuzosin, finasteride and combination therapy, whereas impotence occurred significantly more often with finasteride and in combination therapy. Discontinuation of treatment was higher with alfuzosin than finasteride and lower with alfuzosin compared to combination therapy. Dizziness was the most frequently reported side effect with alfuzosin compared to placebo. Postural hypotension, syncope and somnolence were reported in less than two percent of patients treated

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				with alfuzosin, but more often than with placebo. Withdrawal rates were similar between treatments.
Tsujii et al.[48] (2000) Prazosin 0.5 to 1 mg BID vs terazosin 0.5 to 1 mg BID vs tamsulosin 0.1 to 0.2 QD	RCT, XO Patients with symptomatic BPH	N=121 4 weeks	Primary: Changes from baseline in symptom score, Qmax, average urinary flow rate, PVR and blood pressure Secondary: Not reported	Primary: Terazosin was associated with a significant improvement in four out of nine symptoms compared to tamsulosin (P<0.05). There were significant increases in Qmax with prazosin, and in average urinary flow rate with tamsulosin (P<0.05 for both). There were no significant changes in PVR with any of the treatments. Significant reductions in blood pressure were observed in the hypertensive patients with prazosin, terazosin and tamsulosin (P<0.05 for all). In the normotensive patients, no significant changes in blood pressure were observed with any of the treatments. Secondary: Not reported
Tsai et al.[49] (2007) Group A: Terazosin (generic) 1 to 4 mg QD for 6 weeks (Period 1), followed by terazosin (brand Hytrin®*) 1 to 4 mg QD for 6 weeks (Period 2) vs Group B: Terazosin (brand Hytrin®*) 1 to 4	OL, RCT Adult men in Taiwan newly diagnosed with symptomatic BPH who had not previously received treatment for BPH	N=53 13 weeks	Primary: Change from baseline in IPSS, tolerability Secondary: Not reported	Primary: After two and six weeks, no significant between-product differences were found in mean (SD) decreases from baseline in IPSS total score (generic, 2.46 [0.84] and 2.46 [1.00], respectively; branded, 1.56 [0.60] and 2.87 [0.71]) (P=0.29). After six weeks, the between-product difference in mean (SD) increase from baseline in Qmax was nonsignificant (generic, 2.36 [0.90] mL/s; branded, 2.03 [0.62] mL/s) (P=0.72). A total of 86 treatment emergent adverse events were reported (45 with the generic drug; 41 with the branded drug), all of which were considered by the investigator as non-serious except for one case of acute epididymitis, which occurred with the generic drug. The most common adverse events reported with the generic and branded formulations were dizziness (7/48 [14.6%] and 10/50 [20.0%], respectively) and peripheral edema (1/48 [2.1%] and 3/50 [6.0%]). No significant differences in the prevalence of adverse events were found between the two treatments. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg QD for 6 weeks (Period 1), followed by terazosin (generic) 1 to 4 mg QD for six weeks (Period 2)				
Yang et al.[50] (2007) Terazosin 2 mg QD for 1 week Those patients with continued LUTS after the initial treatment were allocated randomly to: terazosin 2 mg QD for 6 weeks vs terazosin 2 mg QD plus tolterodine 2 mg BID for 6 weeks	RCT Patients diagnosed with LUTS due to BPH	N=69 7 weeks	Primary: Change from baseline in IPSS Secondary: Not reported	Primary: IPSS was significantly improved with both treatments after the initial first week, and the reduction of IPSS with combination therapy was significantly greater compared to terazosin (P<0.01). A decrease in urgency, frequency and nocturia were the main contributory factors causing the reduction of IPSS with combination therapy. Differences in Qmax and residual urine from baseline were noted with both treatments, but there was no difference between the treatments (P values not reported). The incidence of adverse effects with combination therapy was higher compared to terazosin. The most commonly reported adverse effects were mouth dryness, which is associated with anticholinergic drugs such as tolterodine. Secondary: Not reported
Dong et al.[51] (2009) Terazosin vs tamsulosin	MA (12 trials) Patients with BPH	N=2,816 4 weeks	Primary: IPSS, quality of life, Qmax, Qave, residual volume, prostate volume, adverse effects Secondary:	Primary: After four weeks of treatment, tamsulosin demonstrated a significant improvement in IPSS compared to terazosin (WMD, -1.24; 95% CI, -1.98 to -0.51; P=0.0009). There was no significant difference in quality of life between the treatment groups (WMD, -0.04; 95% CI, -0.16 to 0.24), Qmax (WMD, -0.38; 95% CI, -1.18 to 0.41), Qave (WMD, -0.39; 95% CI, -0.84 to 0.06), residual volume (WMD, -4.32; 95% CI, -10.96 to 2.33), or prostate volume

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Not reported	(WMD, -0.28; 95% CI, -3.37 to 2.81). Fewer patients experienced dizziness (RR, 0.38; 95% CI, 0.30 to 0.48), severe hypotension (RR, 0.16; 95% CI, 0.04 to 0.68), and dry mouth (RR, 0.14; 95% CI, 0.03 to 0.77) with tamsulosin compared to patients receiving terazosin. Secondary: Not reported
Lepor et al.[52] (1996) Terazosin 1 to 10 mg QD vs finasteride 5 mg QD vs finasteride 5 mg QD plus terazosin 1 to 10 mg QD vs placebo	DB, MC, RCT Men 45 to 80 years of age with symptomatic BPH	N=1,229 1 year	Primary: Change from baseline in AUA SS and Qmax Secondary: Not reported	Primary: A significantly greater reduction in symptom scores were observed with terazosin and combination therapy compared to finasteride and placebo (6.1, 6.2, 3.2 and 2.6 points respectively; P<0.001 for terazosin vs finasteride, combination therapy vs finasteride, terazosin vs placebo and combination therapy vs placebo). There was no difference in scores noted between terazosin and combination therapy (P=1.00) or finasteride and placebo (P=0.63). Terazosin and combination therapy was also associated with a greater increase in Qmax compared to finasteride or placebo (2.7, 3.2, 1.6 and 1.4 mL/second). Differences between finasteride and terazosin, finasteride and combination therapy, combination therapy and placebo and terazosin and placebo all reached statistical significance (P<0.001 for all comparisons), whereas the difference between terazosin and combination therapy (P=0.15) and finasteride and placebo (P=0.07) did not. Secondary: Not reported
Liu et al.[53] (2009) Terazosin 2 mg/day vs	DB, PG, RCT Men ≥50 years of age with Stage 1 or 2 essential HTN (SBP 140 to 180 mm Hg and/or DBP 90 to 110 mm Hg)	N=360 28 days	Primary: Reduction in the total and sub-scores of the IPPS and blood pressure Secondary: Not reported	Primary: Treatment with terazosin and amlodipine monotherapy led to a similar reduction in the total IPSS (6.7 vs 6.9). There were no significant difference in the reduction in the bladder outlet obstruction sub-score (4.0 vs 4.1), OAB sub-score (2.9 vs 2.6), or quality of life score (1.1 vs 1.2) with amlodipine compared to terazosin. Treatment with terazosin and amlodipine led to a greater reduction in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
amlodipine 5 mg/day vs terazosin 2 mg/day and amlodipine 5 mg/day	and with LUTS (IPSS ≥10)			QOL score (1.4 vs 1.1, P<0.05) compared to amlodipine monotherapy. There was no significant difference in the reduction in the total IPSS (7.8), bladder outlet obstruction sub-score (4.8), or OAB sub-score (3.2) with terazosin and amlodipine compared to amlodipine alone or terazosin alone. The rate of the responders (defined as patients with a reduction of 40% or more in the total IPSS, bladder outlet obstruction sub-score, OAB sub-score, or quality of life score or total IPSS of <8) were similar between the amlodipine group (36.1, 41.2, 46.2, and 33.6%, respectively) and terazosin group (39.3, 46.2, 39.3, and 41.0%, respectively). The rate of responders in the OAB sub-score was significantly greater in the terazosin and amlodipine group than in the terazosin group (53.8 vs 39.3%, P<0.05). The rate of responders in the quality of life score was significantly greater in the terazosin + amlodipine group than in the amlodipine group (47.1 vs 33.6%, P<0.05). The mean reduction in SBP and DBP was greater with amlodipine than terazosin (21.8/10.0 vs 11.9/6.5 mm Hg, P<0.01). The greatest reduction in SBP and DBP (25.2/12.6 mm Hg) occurred in the terazosin and amlodipine group (P<0.01 vs terazosin and P<0.05 vs amlodipine). The rates of blood pressure control were greater in the amlodipine group (63.9%) and the terazosin and amlodipine group (73.1%) than in the terazosin group (36.8%, both P<0.001). Secondary: Not reported
Wilt et al.[54] (2000) Terazosin vs other α-adrenergic blocking agents,	SR (17 trials) Men with symptomatic benign prostatic obstruction	N=5,151 4 to 52 weeks	Primary: Change from baseline in urological symptom scale scores Secondary: Urodynamic	Primary: Boyarsky symptom score improved by 37% with terazosin and by 15% with placebo. AUA SS scores improved by 38% with terazosin compared to 20% with finasteride and 17% with placebo. Terazosin was comparable to tamsulosin (40 and 43%, respectively) in improving IPSS (P values not reported). Secondary: The improvement in Qmax reported with terazosin (22%) was similar to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
finasteride, finasteride plus terazosin or placebo			measures, adverse effects	other α-adrenergic blocking agents, but higher compared to finasteride (15%) and placebo (11%). Side effects, including dizziness, asthenia, headache and postural hypotension, occurred more often with terazosin compared to placebo. Rates of discontinuation with terazosin were higher than other α-adrenergic blocking agents, but similar to finasteride and placebo.
Wilt et al.[55] (2002) Other α-adrenergic blocking agents, Permixon®* or placebo vs tamsulosin 0.2 to 0.8 mg QD	SR (14 trials) Men with BPH and LUTS	N=4,122 4 to 26 weeks	Primary: Change from baseline in urological symptom scale scores Secondary: Changes from baseline in Qmax, adverse effects	Primary: The WMD in the Boyarsky symptom score for tamsulosin compared to placebo was -1.1 points (95% CI, -1.49 to -0.72) or a 12% improvement with 0.4 mg and -1.6 points (95% CI, -2.3 to -1.0) or a 16% improvement with 0.8 mg. Secondary: The WMD in Qmax was 1.1 mL/second with both tamsulosin 0.4 and 0.8 mg (95% CI, 0.59 to 1.51 with 0.4 mg; 95% CI, 0.65 to 1.48 with 0.8 mg). Tamsulosin was reported to be as effective as other α-adrenergic blocking agents or Permixon® in the improvement of LUTS and Qmax. Dizziness, rhinitis and abnormal ejaculation occurred significantly more often with tamsulosin than placebo. The rates of adverse events and withdrawal increased with higher doses of tamsulosin. Terazosin was associated with a higher rate of discontinuation than low dose tamsulosin.
Hypertension				
Hayduk et al.[56] (1987) Doxazosin 1 to 16 mg QD vs terazosin 1 to 20 mg QD	DB, MC, RCT Patients with high blood pressure	N=55 14 weeks	Primary: Proportion of patients achieving blood pressure success and normalization (blood pressure ≤90 mm Hg), safety Secondary: Not reported	Primary: Blood pressure success was higher with doxazosin compared to terazosin (73 vs 64%; P value not reported). Blood pressure normalization was higher with doxazosin compared to terazosin (65 vs 57%; P value not reported). The incidence of treatment-related side effects was higher with terazosin compared to doxazosin (39 vs 30%; P value not reported). Secondary: Not reported
Torvik et al.[57]	DB	N=172	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1986) Doxazosin 1 to 16 mg QD vs prazosin 0.5 to 10 mg BID vs placebo	Patients with essential HTN	12 weeks	Changes from baseline in blood pressure, heart rate, and plasma lipid profiles Secondary: Not reported	Doxazosin and prazosin both produced significant reductions in blood pressure compared to placebo (P<0.05 to P<0.005). There was no significant difference between the three treatments in changes in plasma lipid profiles or heart rate (P values not reported). There was a significant baseline reduction in TG only with doxazosin (P<0.05). Secondary: Not reported
Fukiyama et al.[58] (1991) Doxazosin vs prazosin	DB, MC, RCT Patients with essential HTN	N=126 12 weeks	Primary: Changes from baseline in blood pressure and heart rate Secondary: Not reported	Primary: There was no significant difference between the two treatments in reductions in blood pressure (P=0.7826); however, both treatments produced significant reductions from baseline (P<0.001). No significant changes in heart rate were observed with either treatment (P value not reported). Secondary: Not reported
DePlanque et al.[59] (1991) Doxazosin QD vs prazosin BID	DB, DD, PG Patients with mild or moderate essential HTN not adequately controlled by diuretics and β-blockers	N=43 14 weeks	Primary: Changes from baseline in blood pressure, heart rate and serum lipid levels; calculated CHD risk using the Framingham equation Secondary: Not reported	Primary: There was no difference between the two treatments in changes in SBP (P value not significant), heart rate (P value not significant) or serum lipid levels (P value not reported). Doxazosin was associated with a significantly greater reduction in standing (P=0.01) and supine (P=0.04) DBP compared to prazosin. At the end of the trial, 84.2 and 56.5% of patients receiving doxazosin and prazosin achieved therapeutic success (P value not reported). Doxazosin (P=0.02) was associated with a greater reduction from baseline in the calculated risk of CHD compared to prazosin (P value not significant).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Deger et al.[60] (1986) Prazosin BID vs terazosin QD vs placebo	DB, MC, PC Patients with mild to moderate HTN	N=174 14 weeks	Primary: Changes from baseline in blood pressure and heart rate Secondary: Not reported	Primary: Terazosin was associated with a significant reduction in supine and standing DBP compared to placebo (P≤0.05). Prazosin was not associated with a significant reduction in supine DBP, but was associated with a significant reduction in mean standing DBP compared to placebo (P values not reported). There was no difference in the changes in heart rate between the two treatments (P value not reported). Secondary: Not reported
Ruoff et al.[61] (1986) <u>Study 1:</u> Prazosin vs terazosin vs placebo <u>Study 2:</u> Terazosin vs HCTZ <u>Study 3:</u> Terazosin and	DB, PG, RCT Patients with mild to moderate HTN	Study 1 N=54 Study 2 N=37 Study 3 N=28	Primary: Blood pressure, pulse rate, body weight, laboratory tests, physical examinations, ECG Secondary: Not reported	Primary: Study 1- There was no significant difference in blood pressure changes between the terazosin and prazosin treatment groups. Study 2- HCTZ produced a significantly greater reduction in supine DBP compared to terazosin. There were no significant differences in standing blood pressure between the HCTZ and terazosin treatment groups. Study 3- There were no significant differences in blood pressure between the treatment groups. The drug treatments did not produce significant changes in pulse rates, body weights, laboratory test results, physical examinations, or electrocardiograms. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
HCTZ vs prazosin and HCTZ				
Neaton et al.[62] (1993) TOMHS Doxazosin 2 to 4 mg QD vs chlorthalidone 15 to 30 mg QD vs acebutolol 400 mg QD vs amlodipine 5 mg QD vs enalapril 5 to 10 mg QD vs placebo	DB, MC, PC, RCT Patients with mild HTN (DBP <100 mm Hg)	N=902 4.4 years	Primary: Blood pressure, quality of life, side effects, blood lipid levels and analysis of other serum components, echocardiographic changes, and incidence of cardiovascular events Secondary: Not reported	Primary: There was a significant reduction in blood pressure in all the active treatment groups compared to placebo (-15.9 vs -9.1 mm Hg for SBP and -12.3 vs -8.6 mm Hg for DBP; P<0.0001). There were no major differences in blood pressure lowering between the 5 active treatment groups (P=0.10). TC was significantly reduced more in the doxazosin group than in the amlodipine, chlorthalidone, and placebo groups (P<0.01). The reduction in LDL-C was significantly more in doxazosin group than in the amlodipine, chlorthalidone, and placebo groups. Reduction in TG was significantly larger with the doxazosin, enalapril, and amlodipine groups than acebutolol group (P<0.01). The lowest level of fasting insulin was observed with doxazosin; fasting insulin was lower than placebo in all drug groups. Secondary: Not reported
Liebson et al.[63]	DB, PC, RCT	N=844	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1995) TOMHS Doxazosin vs chlorthalidone vs acebutolol vs amlodipine vs enalapril vs placebo	Patients with mild HTN	4 years	Changes in blood pressure and pulse, changes in left ventricular mass from baseline to end of study period as assessed by ECG Secondary: Not reported	All drug treatment groups showed significantly greater reduction of blood pressure compared to placebo (mean decrease of 16/12 vs 9/9 mm Hg; P<0.001). Pulse rate decreased by 10 bpm for the acebutolol group compared to 1 to 3 bpm for the other treatment groups. All drug treatment groups and the placebo group showed significant decreases (10 to 15%) in left ventricular mass. The chlorthalidone group showed the largest decrease in left ventricular mass at 34 g compared to 24 to 27 g for the other treatment groups. Secondary: Not reported
Brown et al.[64] (1995) <u>Study A:</u> Doxazosin, followed by amlodipine, followed by doxazosin and amlodipine vs	DB, RCT, XO Patients with moderate or severe HTN	N=24 18 weeks	Primary: Blood pressure and heart rate, foot volume as measure of edema, plasma noradrenaline concentration Secondary: Not reported	Primary: <u>Study A:</u> The decrease in blood pressure was significantly greater than the sum of the blood pressure falls at the end of the single drug treatment periods. The reduction in blood pressure was greater with amlodipine than doxazosin (P<0.01). The reduction in blood pressure was greater with combination than amlodipine (P<0.001). No significant changes in heart rate were observed. One subject developed ankle edema. The plasma noradrenaline concentration did not change significantly during the single drug treatment periods, but doubled at the end of the combination treatment period (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Study B: Enalapril, followed by amlodipine, followed by enalapril and amlodipine				Study B: The reduction in blood pressure was significantly greater with amlodipine than enalapril (P<0.05). The reduction in blood pressure was significantly greater with combination than amlodipine (P<0.05) with the exception of erect blood pressure. No significant changes in heart rate were noted. No significant difference in foot volume was observed between treatments. The plasma noradrenaline was significantly higher than at baseline (P<0.01). Secondary: Not reported
Deary et al.[65] (2002) Doxazosin 1 to 4 mg/day vs amlodipine 5 mg/day vs lisinopril 2.5 to 10 mg/day vs bisoprolol 5 mg/day vs bendro-flumethiazide* 2.5	DB, XO Hypertensive patients, aged 18 to 55 years old	N=34 42 weeks (6 week treatment of each drug or placebo, then the 7th week was a repeat of each patient's most effective, tolerated drug)	Primary: Blood pressure, heart rate Secondary: Not reported	Primary: All drug treatments caused significant decreases in blood pressure. Bendroflumethiazide performed significantly worse (P=0.0016) and bisoprolol performed significantly better (P=0.004) than amlodipine. When the most effective drugs for each patient were tabulated, all drugs included in the study except for bendroflumethiazide, were represented. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day vs placebo				
Hayduk et al.[66] (1987) <u>Study 1:</u> Doxazosin 1 to 16 mg QD vs prazosin 1 to 20 mg BID vs HCTZ 25 to 100 mg QD vs nadolol 40 to 160 mg QD vs atenolol 50 to 100 mg QD vs metoprolol 100 to 200 mg BID	DB, MC Patients with HTN	<u>Study 1:</u> N=903 10 to 24 week trial; therapy continued for up to 62 weeks <u>Study 2:</u> N=52 12 weeks	Primary: Blood pressure, heart rate Secondary: Not reported	Primary: Blood pressure lowering effect of doxazosin was similar to that of the other antihypertensive drugs. There was no significant difference in the heart rate with the doxazosin treated group. The β-blockers demonstrated clinically significant bradycardia. Both doxazosin and terazosin were equally efficacious, but doxazosin was effective at significantly lower doses. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo <u>Study 2:</u> Doxazosin 16 mg QD vs terazosin 20 mg QD				
Trost et al.[67] (1987) Doxazosin 1 to 16 mg QD vs HCTZ 25 to 100 mg QD	DB, MC, PG Patients with HTN	N=104 6 months	Primary: Blood pressure, serum lipid changes Secondary: Not reported	Primary: There was no significant difference in the supine and standing blood pressures between the two treatment groups. There was significantly greater reduction in total TG (P=0.002) and TC concentration (P=0.006) and significantly greater increase in HDL-C:TC (P=0.001) in the doxazosin arm compared to the HCTZ arm. Secondary: Not reported
Grimm et al.[68] (1996) Doxazosin 2 to 16 mg vs HCTZ 25 to 50 mg	DB, PG, RCT Patients with HTN	N=107 1 year	Primary: Blood pressure, heart rate, biochemistries, lipids/lipoproteins, quality of life, ECGs, adverse effects Secondary: Not reported	Primary: There were no significant differences in blood pressure lowering, heart rate, quality of life measures, or serious adverse effects between the two treatment groups. The doxazosin treated group experienced a more favorable high density lipoprotein /total cholesterol ratio (P≤0.01) compared to the hydrochlorothiazide group. Both drug treatments showed significant reduction in left ventricular mass (P<0.001) and wall thickness (P<0.05). The left ventricular systolic and diastolic internal dimensions were significantly less in the HCTZ group compared to the doxazosin group. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Ferrara et al.[69] (1993) Doxazosin 1 to 16 mg QD vs captopril 25 to 150 mg QD	MC, OL, PG Patients with hyper-cholesterolemia and HTN	N=224 14 weeks	Primary: Blood pressure (normalized blood pressure defined as standing diastolic pressure ≤90 mm Hg), serum lipid levels, quality of life Secondary: Not reported	Primary: Blood pressure was significantly reduced with both drugs (P<0.001). A total of 73% of the doxazosin group and 67% of the captopril group achieved normalized blood pressure. Serum TC level was significantly improved with both drugs (P<0.001). The HDL-C concentration was only significantly increased in the doxazosin group (P<0.001). The calculated 10-year risk for the development of CHD was significantly reduced with both drug treatments (P<0.001). Secondary: Not reported
Derosa et al.[70] (2005) Doxazosin 4 mg QD vs irbesartan 300 mg QD	DB, PG, RCT Patients with type 2 diabetes and mild HTN	N=96 1 year	Primary: Blood pressure, glucose metabolism, lipid parameters Secondary: Not reported	Primary: Blood pressure was significantly reduced in both treatment groups compared to baseline (P<0.01). Irbesartan was significantly better in lowering blood pressure compared to doxazosin (P<0.05). Doxazosin significantly reduced glycosylated hemoglobin, fasting plasma glucose, fasting plasma insulin, TC, LDL-C, HDL-C, and TG (P≤0.05 for all parameters). As monotherapy, neither of the drugs achieved adequate blood pressure control. Secondary: Not reported
Taylor et al.[71] (1988) Doxazosin 1 to 16 mg QD	DB, PG Patients with mild or moderate essential HTN	N=67 18 weeks	Primary: Blood pressure (therapeutic success defined as standing DBP ≤90	Primary: A total of 74% of the doxazosin group achieved therapeutic success compared to 81% of the enalapril group. Blood pressures were significantly reduced in both groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs enalapril 10 to 40 mg QD			mm Hg), lipid parameters Secondary: Not reported	There were no significant changes in the lipid profile observed for either drug. Secondary: Not reported
Wessels et al.[72] (1991) Doxazosin QD vs enalapril QD	DB, DD, PC, RCT Patients with mild or moderate essential HTN	N=54 12 weeks	Primary: Blood pressure, heart rate, serum lipid profile, calculated CHD risk Secondary: Not reported	Primary: Both drugs produced significant reductions in blood pressure (P<0.05). There was no significant change in heart rate with both drugs. Doxazosin showed a significant reduction in the total serum cholesterol concentration (P<0.05). Doxazosin also showed a decrease in triglyceride level (P value not significant) and an increase in HDL-C/total cholesterol ratio (P value not significant). Coronary heart disease risk reduction was significant and greater in the doxazosin group compared to the enalapril group (-27.58 vs -18.49%, P<0.02). Secondary: Not reported
Hjortdahl et al.[73] (1987) Doxazosin QD vs HCTZ QD	DB, RCT Patients with mild to moderate essential HTN	N=115 24 weeks	Primary: Blood pressure, heart rate, lipid profile, side effects Secondary: Not reported	Primary: There was no significant difference between treatment groups for blood pressure and heart rate except HCTZ produced significantly greater supine SBP than doxazosin (P=0.04). There were significant reductions in TC (P=0.006) and total TG (P=0.018) for the doxazosin group. Eleven patients of the HCTZ group had an abnormally low potassium level and seven of the HCTZ treated group had abnormally high uric acid concentrations. Secondary: Not reported
Ott et al.[74]	DB, MC, RCT	N=126	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1987) Doxazosin 1 to 16 mg QD vs atenolol 50 to 100 mg QD	Patients with mild to moderate HTN	20 weeks	Blood pressure, heart rate Secondary: Not reported	There was no significant difference between treatment groups in blood pressure. Both drugs reduced heart rate, but atenolol produced a significantly greater decrease in heart rate than doxazosin (P<0.001). Secondary: Not reported
Frick et al.[75] (1986) Doxazosin 1 to 16 mg QD vs atenolol 50 to 100 mg QD	DB, DD, MC, RCT Patients with mild to moderate essential HTN	N=152 1 year	Primary: Blood pressure, heart rate, lipid profile Secondary: Not reported	Primary: At endpoint, there was greater blood pressure reduction with atenolol than doxazosin. This was statistically significant only in the supine position (P<0.05). Doxazosin reduced the heart rate slightly, while atenolol produced a marked bradycardia (P<0.0001). HDL-C:TC was raised in the doxazosin group and lowered in the atenolol group (P=0.001). TG levels decreased in the doxazosin group and increased in the atenolol group (-5.0 vs 42.7%; P<0.001). Secondary: Not reported
Daae et al.[76] (1998) Doxazosin QD vs atenolol QD	DB, MC, PG Patients with mild to moderate HTN	N=228 1 year followed by a 4-year OL, ES	Primary: Blood pressure, heart rate, lipid profile, calculated risk of developing CHD in 10 years using the Framingham equation Secondary: Not reported	Primary: Both groups showed similar decreases in blood pressure. The doxazosin-treated group had a significantly greater reduction from baseline in CHD risk than the atenolol-treated group (P<0.05). TC significantly decreased from baseline in both treatment groups (P≤0.05), with no statistically significant difference between the groups. HDL-C (P<0.01), the HDL-C:TC (P<0.01), and TG levels (P<0.01) significantly improved in the doxazosin group compared to the atenolol group. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Talseth et al.[77] (1991) Doxazosin (mean dose used: 5.2 mg QD) vs atenolol (mean dose used: 66.4 mg QD)	PG, RCT Patients with mild and moderate HTN	N=164 3 years	Primary: Blood pressure, heart rate, lipids profile, calculated CHD risk using the Framingham equation Secondary: Not reported	Primary: Both drugs produced similar reductions in blood pressure. Atenolol produced a significant decrease in heart rate (P<0.05), while doxazosin did not change the heart rate significantly. Doxazosin significantly reduced TG levels (P<0.001), increased HDL-C levels (P<0.001), and increased the HDL-C:TC (P<0.001) compared to atenolol. The calculated CHD risk was significantly increased with atenolol (P<0.05) and significantly decreased with doxazosin (P<0.05) from baseline. Secondary: Not reported
Carruthers et al.[78] (1993) Doxazosin QD vs atenolol QD	RCT Patients with mild to moderate systemic HTN and normal serum lipid	N=191 24 weeks	Primary: Calculated CAD risk using the Framingham formula Secondary: Not reported	Primary: Doxazosin treatment produced a significantly greater reduction in CHD risk compared to atenolol (P=0.0074). The relative risk of CHD was reduced to 0.92 in the atenolol group (P=0.144) and 0.74 in the doxazosin group (P=0.0001) from baseline. Secondary: Not reported
Searle et al.[79] (1990) Doxazosin 11 mg (mean dose) vs placebo All patients	DB, MC, RCT Patients with mild to moderate essential HTN	N=87 12 weeks	Primary: Changes from baseline in blood pressure, heart rate and serum lipids Secondary: Not reported	Primary: Doxazosin was associated with significant reductions in blood pressure compared to placebo (17.0/12.3 vs 6.2/6.7 mm Hg; P<0.05). The supine blood pressure was decreased by 13.2/9.8 mm Hg with doxazosin compared to 9.2/6.0 mm Hg with placebo (P value not reported). Only minor, nonsignificant changes in serum lipids and heart rate were observed between the two treatments (P value not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
received atenolol 100 mg/day.				
Ohta et al.[80] (2007) Doxazosin 1 to 2 mg QD to BID Treatment was added to calcium channel blockers, ARBs and ACE inhibitors.	RETRO Patients with HTN that had poorly controlled blood pressure	N=41 3 months (mean follow up 170 days)	Primary: Changes from baseline in blood pressure and blood chemistry Secondary: Not reported	Primary: Blood pressure decreased from 152±14/81±12 to 135±14/70±11 mm Hg after the addition of doxazosin at a mean dose of 1.5 mg/day (P<0.001). When good SBP control was defined as <140 mm Hg, the prevalence of patients with good SBP control increased from 24 to 61% with the addition of doxazosin (P<0.01). Similarly, the prevalence of patients with good DBP control (<90 mm Hg) increased from 78 to 98% (P<0.01). Patients whose SBP decreased >10 mm Hg (n=25) showed significantly higher baseline SBP, TC and LDL-C compared to those who showed less SBP reduction (<10 mm Hg; P<0.01). Comparable reductions in blood pressure were obtained between obese patients (BMI ≥25, change in blood pressure at three months: -15±15/-12±9 mm Hg, n=18) and non-obese patients (-14±19/-7±8 mm Hg, n=23). Secondary: Not reported
de Alvaro et al.[81] (2006) ASOCIA Doxazosin SR 4 mg QD, increased to 8 mg/day at week 4 if required Added to entry medication.	MC, PRO Patients with HTN (>140/>90 mm Hg) on previous antihypertensive medication who were uncontrolled	N=3,631 16 weeks	Primary: Proportion of patients achieving goal blood pressure (<140/<90 mm Hg), adverse events Secondary: Not reported	Primary: The proportion of patients achieving goal blood pressure after four weeks of add on therapy with doxazosin was 39% and increased to 61% after 16 weeks. SBP and DBP (mean±SEM) decreased, respectively, from 161.6 ±0.2/95.1±0.1 mm Hg at baseline to 142.2±0.2/84.1±0.1 mm Hg after four weeks (P<0.0001) and to 136.8±0.2/80.6±0.2 mm Hg after 16 weeks (P<0.0001). Adverse events occurred in 108 patients (3.0%), with 57 (1.6%) related to the study treatment. In 17 patients (0.5%), serious adverse events were described, but only one was related to the study drug. Secondary: Not reported
Os et al.[82] (2006)	DB, PG, RCT	N=310	Primary: Efficacy, safety	Primary: All groups had a significant decrease in blood pressure at all study visits

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Doxazosin 4 mg QD vs doxazosin 2 mg QD vs doxazosin SR 4 mg QD	Patients 18 to 80 years of age with mild to moderate essential HTN (sitting DBP 95 to 110 mm Hg and SBP <180 mm Hg)	9 weeks	Secondary: Not reported	compared to baseline. The proportion of patients who reached goal sitting DBP (<90 mm Hg) was similar among the three treatment groups, except at week one, when more patients in the doxazosin SR group had obtained the goal compared to those in the doxazosin 2 mg group (40.6 vs 22.3%; P=0.005). The proportion of patients who reached sitting SBP (<140 mm Hg) goal was similar among groups. Adverse event profiles among the groups were similar. Secondary: Not reported
Williams et al.[83] (2015) PATHWAY-2 Twelve weeks of once daily treatment with each of spironolactone (25 to 50 mg), bisoprolol (5 to 10 mg), doxazosin modified release (4 to 8 mg), and placebo, in addition to their baseline blood pressure drugs	DB, PC, XO Patients 18 to 79 years of age with seated clinic SBP ≥ 140 mmHg (or ≥135 mmHg for patients with diabetes) and home SBP (18 readings over four days) ≥130 mmHg, despite treatment for at least three months with maximally tolerated doses of three drugs (an ACE or ARB, a CCB, and a diuretic)	N=335 12 months	Primary: Average home SBP, recorded in the morning and the evening in triplicate, on four consecutive days before study visits Secondary: Clinic SBP, BP control rates, adverse events	Primary: The average reduction in home SBP by spironolactone was significantly greater compared to placebo (–8.70 mmHg; 95% CI, −9.72 to −7.69; P<0.0001), compared to the mean of the other two active treatments (doxazosin and bisoprolol; −4.26; 95% CI, –5.13 to −3.38; P<0·0001), and compared to the individual treatments; versus doxazosin (–4.03; 95% CI, –5.04 to −3.02; P<0.0001) and versus bisoprolol (–4.48; 95% CI, –5.50 to −3.46; P<0.0001). Secondary: The results for seated clinic SBP largely mirror those seen with home SBP except that there was a large placebo effect on clinic BP that was not seen with home BP measurement. Overall 219 (68.9%; 95% CI, 63.6 to 73.8) of 314 patients achieved target home SBP of <135 mmHg. 58% of patients had their BP controlled with spironolactone, which was significantly greater than rates for other treatments (P<0.001 when compared to doxazosin, bisoprolol, and placebo). Most patients who were controlled by doxazosin or bisoprolol had a still greater fall in blood pressure on spironolactone, which was consequently the most effective treatment in almost 60% of patients. This was at least three times the proportion in whom doxazosin or bisoprolol were the most effective.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				All active treatments were well tolerated with similar low rates of adverse events and withdrawals due to adverse events.
Materson et al.[84] (1994) Prazosin 4 to 20 mg QD vs HCTZ 12.5 to 50 mg QD vs atenolol 25 to 100 mg QD vs captopril 25 to 100 mg QD vs clonidine 0.2 to 0.6 mg QD vs diltiazem SR 120 to 360 mg QD vs placebo	DB, MC, RCT Men with DBP of 95 to 109 mm Hg	N=1,292 1 year	Primary: Success as defined by DBP ≤95 mm Hg at 1 year Secondary: Not reported	Primary: Success rates were 59% for diltiazem, 51% for atenolol, 50% for clonidine, 46% for HCTZ, 42% for captopril, 42% for prazosin, and 25% for placebo (P<0.001 between diltiazem and HCTZ, atenolol and prazosin). The rates of adverse effects leading to termination of treatment were highest with prazosin at 13.8% and clonidine at 10.1%, which was significantly different from captopril at 4.8%, atenolol at 2.2%, HCTZ at 1.1%, diltiazem at 5.5%, and placebo at 6.4%. Successful blood pressure control was highest with diltiazem at 64% in African Americans, highest with captopril at 55% in younger whites, and highest with atenolol at 68% in older whites. Secondary: Not reported
McAreavey et al.[85]	DB, PG, RCT	N=238	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1984) Prazosin 0.5 mg QD up to 10 mg BID vs hydralazine 12.5 mg QD up to 100 mg BID vs labetalol 200 mg QD up to 1,600 mg BID vs methyldopa 125 mg QD up to 1,000 mg BID vs placebo Minoxidil as add on therapy was given to men only. Doses were titrated upward at 2 week intervals until target BP or maximum dose	Patients with inadequately controlled HTN while receiving atenolol 100 mg/day and bendrofluazide* 5 mg/day	6 months	Comparative safety and efficacy, target blood pressure <140/95 mm Hg Secondary: Not reported	Target blood pressure was reached in 25% of patients receiving hydralazine, 23% of patients receiving minoxidil, 19% of patients receiving prazosin, 17% of patients receiving methyldopa and zero percent of patients receiving placebo (P values not reported). Labetalol had the highest withdrawal rate compared to the other treatments with 78% (P<0.05). Minoxidil had the second highest withdrawal rate with 57% (P<0.05), due to fluid retention. There were no significant differences in withdrawal rates among the other treatments. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
was reached.				
Chrysant et al.[86] (1986) Terazosin vs placebo	DB, MC, PC, RCT Patients with inadequate control of essential HTN	N=138 Duration not specified	Primary: Changes from baseline in blood pressure, physical examination and ECG Secondary: Not reported	Primary: There was a significant mean reduction in supine DBP with the terazosin compared to placebo (7.3 vs 0.6 mm Hg; P<0.05). There were no significant changes between treatments in physical examinations or ECGs. Secondary: Not reported
Holtzman et al.[87] (1988) Terazosin vs placebo in combination with atenolol	DB, MC, PC Patients with HTN	N=92 10 weeks	Primary: Changes from baseline in blood pressure and lipid profiles Secondary: Not reported	Primary: There was a significant reduction in supine and standing blood pressure (P<0.05), TC (P<0.05) and LDL-C plus VLDL-C (P<0.05) with terazosin. Secondary: Not reported
Casas et al.[88] (2005) ACE inhibitor or ARBs compared to other antihypertensive drugs (β-adrenergic blocking agents, α-adrenergic blocking agents, calcium-channel blocking agents, or combinations) vs	MA (127 trials) Studies in adults that examined the effect of any drug treatment with a blood pressure lowering action on progression of renal disease	N=not reported 4.2 years (mean)	Primary: Doubling of serum creatinine, and ESRD Secondary: Serum creatinine, urine albumin excretion and GFR	Primary: Treatment with ACE inhibitors or ARBs resulted in a nonsignificant reduction in the risk of doubling of creatinine vs other antihypertensives (P=0.07) with no differences in the degree of change of SBP or DBP between the groups. A small reduction in ESRD was observed in patients receiving ACE inhibitors or ARBs compared to other antihypertensives (P=0.04) with no differences in the degree of change of SBP or DBP between the groups. Secondary: Small reductions in serum creatinine and in SBP were noted when ACE inhibitors or ARBs were compared to other antihypertensives (P=0.01). Small reduction in daily urinary albumin excretion in favor of ACE inhibitor or ARBs were reported when these agents were compared to other antihypertensives (P=0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ACE inhibitor or ARBs compared to placebo Specific agents and doses were not specified.				Compared to other drugs, ACE inhibitors or ARBs had no effect on the GFR.
Outcomes Trials				
ALLHAT[89-91] (2000, 2003, 2004) Doxazosin 2 to 8 mg QD vs chlorthalidone 12.5 to 25 mg QD	AC, DB, RCT Patients ≥55 years of age with HTN and ≥1 CHD risk factor	N=24,335 3.3 years	Primary: Combined occurrence of CHD death or nonfatal MI Secondary: All-cause mortality, stroke, combined CHD (CHD death, nonfatal MI, revascularization procedures and hospitalized angina), stroke, combined cardiovascular disease (CHD death, nonfatal MI, stroke, revascularization procedures, angina, CHF and PAD)	Primary: There was no difference in risk of the combined primary endpoint between the two treatments (P=0.71). Secondary: There was no difference in risk of all-cause mortality between the two treatments (P=0.71). Compared to chlorthalidone, doxazosin was associated with a significantly higher risk of stroke (RR, 1.19; 95% CI, 1.01 to 1.40; P=0.04) and combined cardiovascular disease (RR, 1.25; 95% CI, 1.17 to 1.33; P<0.001). The risk of CHF doubled with doxazosin compared to chlorthalidone (P<0.001). Doxazosin was associated with a significantly higher risk of angina (RR, 1.16; P<0.001) and coronary revascularization (RR, 1.15; P=0.05). No difference between the two treatments were observed for risk of PAD (RR, 1.07; P=0.50)
Wright et al.[92] (2008) ALLHAT	DB, RCT Hypertensive individuals with and	N=42,418 3.2 years (median	Primary: Fatal CHD or nonfatal MI	Primary: No differences were noted among the four treatment groups, regardless of race or metabolic/cardiometabolic syndrome status for the primary end point (fatal CHD or nonfatal MI).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Doxazosin vs chlorthalidone vs amlodipine vs lisinopril	without metabolic/ cardiometabolic syndrome	follow-up)	Secondary: Heart failure, combined cardiovascular disease, stroke, ESRD	Secondary: Significantly higher rates of heart failure were consistent across all treatment comparisons in those with metabolic/cardiometabolic syndrome. RRs were 1.50 (95% CI, 1.18 to 1.90), 1.49 (1.17 to 1.90), and 1.88 (1.42 to 2.47) in African American participants and 1.25 (1.06 to 1.47), 1.20 (1.01 to 1.41), and 0.82 (1.51 to 2.19) in non-African American participants for amlodipine, lisinopril, and doxazosin comparisons with chlorthalidone, respectively. Higher rates for combined cardiovascular disease were observed with lisinopril and chlorthalidone (RR, 1.24; 95% CI, 1.09 to 1.40; RR, 1.10; 95% CI, 1.02 to 1.19, respectively) and doxazosin and chlorthalidone comparisons (RR, 1.37; 95% CI, 1.19 to 1.58; RR, 1.18; 95% CI, 1.08 to 1.30, respectively) in African American and non-African American participants with metabolic/cardiometabolic syndrome. Higher rates of stroke were seen in African American participants only (RR, 1.37; 95% CI, 1.07 to 1.76 for the lisinopril and chlorthalidone comparison, and RR, 1.49; 95% CI, 1.09 to 2.03 for the doxazosin and chlorthalidone comparison). African American patients with metabolic/cardiometabolic syndrome also had higher rates of end-stage renal disease (RR, 1.70; 95% CI, 1.13 to 2.55) with lisinopril compared to chlorthalidone.
Dahlöf et al.[93] (2005) ASCOT-BPLA Amlodipine 5 to 10 mg and if needed perindopril 4 to 8 mg or atenolol 50 to 100	MC, RCT Patients with HTN	N=19,257 5.5 years	Primary: Nonfatal MI and fatal CHD Secondary: Nonfatal MI, and fatal CHD, total coronary endpoint, total cardiovascular events and procedures, all-cause mortality, cardiovascular	Primary: The trial was halted early due to findings that patients on the amlodipine and perindopril regimen had fewer of the primary endpoints (P=0.1052) and lower rates of fatal and nonfatal stroke (P=0.0003), total cardiovascular events and procedures (P<0.0001), all-cause mortality (P=0.025), and incidence of developing diabetes (P<0.0001). There was a greater reduction in blood pressure by an average of 2.7/1.9 mm Hg in the amlodipine-based regimen compared to the atenolol-based regimen. There was no significant difference in the percent of patients (25%) that stopped therapy because of an adverse event between the two treatment

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg and if needed bendro-flumethiazide* 1.25 to 2.5 mg If goal blood pressure was still not achieved, doxazosin 4 to 8 mg was added to the regimen.			mortality, fatal and nonfatal stroke, fatal and nonfatal heart failure, silent MI, unstable angina, chronic stable angina, PAD, life-threatening arrhythmias, development of diabetes mellitus, development of renal impairment	groups. However, a significantly greater proportion of patients in the amlodipine-based regimen stopped the trial therapy early because of serious adverse events compared to the atenolol-based regimen (P<0.0001). Secondary: Patients on the amlodipine-perindopril regimen had fewer fatal and nonfatal strokes (P=0.0003), total cardiovascular events and procedures (P<0.0001), and all-cause mortality (P=0.025). Patients on the amlodipine and perindopril regimen had less chance of developing diabetes (P<0.0001).
Chapman et al.[94] (2007) ASCOT-BPLA Atenolol 50 to 100 mg titrated to target blood pressure <140/90 mm Hg (or <130/90 mm Hg in diabetic patients); bendro-flumethiazide* plus potassium 1.25 to 2.5 mg plus doxazosin were added for additional blood pressure control; if blood pressure remained elevated on the 3 above drugs,	Subanalysis of ASCOT-BPLA evaluating effects of spironolactone on treatment-resistant HTN Patients 40 to 79 years of age with HTN and ≥3 cardiovascular risk factors, with SBP ≥160 mm Hg and/or DBP ≥100 mm Hg (not on antihypertensive therapy) or SBP ≥140 mm Hg and/or DBP ≥90 mm Hg (on antihypertensive therapy)	N=1,411 1.3 years	Primary: Change in DBP and SBP, adverse effects Secondary: Not reported	Primary: Spironolactone-treated patients lead to a significant 21.9 mm Hg reduction in SBP among patients whose blood pressure was previously uncontrolled on at least three other antihypertensive drugs (95% CI, 20.8 to 23.0 mm Hg; P<0.001). Spironolactone-treated patients lead to a significant 9.5 mm Hg reduction in DBP among patients whose blood pressure was previously uncontrolled on at least three other antihypertensive drugs (95% CI, 9.0 to 10.1; P<0.001). Spironolactone-treated patients exhibited small but significant decreases in sodium, LDL-C and TC as well as increases in potassium, glucose, creatinine and HDL-C (P<0.05). The most common adverse effect reported in the trial was gynecomastia in men (P value not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
spironolactone 25 mg was added to the regimen vs amlodipine 5 to 10 mg titrated to target blood pressure <140/90 mm Hg (or <130/90 mm Hg in diabetic patients); perindopril 4 to 8 mg and doxazosin were added for additional control; if blood pressure remained elevated on the 3 above drugs, spironolactone 25 mg was added to the regimen				

*Agent not available in the United States.
Drug regimen abbreviations: BID=twice daily, IR=immediate-release, QD=once daily, QID=four times daily, SR=sustained-release, TID=three times daily
Study design abbreviations: AC=active comparator, DB=double blind, DD=double dummy, MA=meta analysis, MC=multicenter, OL=open label, PC=placebo controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, SR=systematic review, XO=cross over
Miscellaneous abbreviations: AUA-SS=American Urology Association Symptom Score, BPH=benign prostatic hyperplasia, CAD=coronary artery disease, CHD=coronary artery disease, CHF=congestive heart failure, CI=confidence interval, DBP=diastolic blood pressure, ECG=electrocardiogram, ESRD=end stage renal disease, GFR=glomerular filtration rate, HCTZ=hydrochlorothiazide, HDL-C=high-density lipoprotein cholesterol, HTN=hypertension, IIEF=International Index of Erectile Function, IPSS=International Prostate Symptom Score, LDL-C=low-density lipoprotein cholesterol, LUTS=lower urinary tract symptoms, MI=myocardial infarction, OAB=overactive bladder, OR=odds ratio, PAD=peripheral artery disease, PSA=prostate-specific antigen, PVR=post-void residual urine volume, Qave=average urinary flow rate, Qmax=maximum urinary flow rate, RR=relative risk, SBP=systolic blood pressure, SD=standard deviation, SEM=standard error of mean, SFAQ= Sexual Function Abbreviated Questionnaire, TC=total cholesterol, TG=triglycerides, TPV=total prostate volume, VLDL-C=very low-density lipoprotein cholesterol, WMD=weighted mean difference

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 9. Relative Cost of the Alpha-Adrenergic Blocking Agents

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Doxazosin	extended-release tablet, tablet	Cardura®*, Cardura XL®	$$$$$	$
Prazosin	capsule	Minipress®*	$$$$$	$
Terazosin	capsule	N/A	N/A	$

*Generic is available in at least one dosage form or strength.
N/A=not available

X. Conclusions

The alpha-adrenergic blocking agents are approved for the treatment of benign prostatic hyperplasia (BPH) and hypertension.[1-6] All of the agents are available in a generic formulation. Treatment guidelines on the management of BPH recommend the use of an α-adrenergic blocking agent or a 5α-reductase inhibitor in patients with moderate-to-severe symptoms. Alpha-blockers can quickly improve symptoms and flow rate, while the 5α-reductase inhibitors have the potential for long-term reduction in prostate volume.[8,9] Available data suggests that the combination is also effective. Clinical trials have demonstrated similar efficacy among the various α-adrenergic blocking agents for the treatment of BPH.[26-55]

There are several national and international organizations that have published guidelines on the treatment of hypertension. Most of the guidelines do not address the use of the α-adrenergic blocking agents.[17-25] Thiazide-type diuretics are frequently recommended as initial therapy in patients with uncomplicated hypertension. According to the National Heart, Lung, and Blood Institute's Eighth Report of The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8), thiazide-type diuretics should be utilized first-line for most patients with hypertension, either alone or in combination with another antihypertensive from a different medication class (e.g., ACE inhibitors, ARBs, β-blockers, calcium channel blockers).[17] Several guidelines consistently recommend that the selection of an antihypertensive agent be based on compelling indications for use.[17-22] Most patients will require more than one antihypertensive medication to achieve blood pressure goals.[17-23]

Several clinical trials have demonstrated that the α-adrenergic blocking agents effectively lower blood pressure when administered as monotherapy or in combination with other antihypertensive agents. Comparative studies have demonstrated similar efficacy when the α-blockers were directly compared to each other, as well as when they were compared to ACE inhibitors, β-blockers, calcium-channel blocking agents and thiazide-type diuretics.[56-88] The ALLHAT trial evaluated the effects of doxazosin on cardiovascular morbidity and mortality. Treatment with doxazosin increased the risk of stroke and cardiovascular events; however, it provided other benefits including improvements in insulin resistance and lipid parameters.[89-92]

There is insufficient evidence to support that one brand alpha-adrenergic blocking agent is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand alpha-adrenergic blocking agents within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand alpha-adrenergic blocking agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Beta-Adrenergic Blocking Agents
AHFS Class 242400
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I. Overview

The beta-adrenergic blocking agents (β-blockers) are approved for the treatment of angina, arrhythmias, essential tremor, heart failure, hypertension, hypertrophic aortic stenosis, migraine prophylaxis, myocardial infarction, and pheochromocytoma.[1-4] Additionally, propranolol is the first agent Food and Drug Administration-approved for the treatment of proliferating infantile hemangioma requiring systemic therapy.[1,2,5] The β-blockers differ with regards to their adrenergic-receptor blocking, membrane stabilizing and intrinsic sympathomimetic activities, as well as lipophilicity.[1-4] There are at least three distinct types of β receptors distributed throughout the body (β_1, β_2, and β_3). β_1 receptors are located predominantly in the heart and kidneys. β_2 receptors are located in the lungs, gastrointestinal tract, liver, uterus, vascular smooth muscle, and skeletal muscle. β_3-receptors are located in fat cells. β-blockers primarily exert their effects through a blockade of β_1 and β_2 receptor subtypes. Agents that have a greater affinity for β_1 receptors are considered to be cardioselective. These agents may be safer in patients with asthma, chronic obstructive pulmonary disease, and peripheral vascular disease because they produce less inhibition of β_2 receptors, which mediate vasoconstriction and bronchospasm. Cardioselectivity is dose dependent; therefore, β_2 blockade can occur at higher doses with these agents.[4,6] Carvedilol and labetalol also block α-adrenergic receptors, which would be expected to reduce peripheral vascular resistance to a greater extent than other β-blockers.[4,6]

The β-blockers are available as single entity agents, as well as fixed-dose combination products. Each of the combination products contains a thiazide-type diuretic. The thiazide-type diuretics inhibit the reabsorption of sodium and chloride in the cortical thick ascending limb of the loop of Henle and the early distal tubules. This action leads to an increase in the urinary excretion of sodium and chloride.[1-3]

The β-adrenergic blocking agents that are included in this review are listed in Table 1 and comparative information on cardioselectivity is highlighted in Table 2. This review encompasses all dosage forms and strengths. All of the agents are available in a generic formulation, with the exception of penbutolol. This class was last reviewed in May 2022.

Table 1. Beta-Adrenergic Blocking Agents Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Acebutolol	capsule	N/A	acebutolol
Atenolol	tablet	Tenormin®*	atenolol
Betaxolol	tablet	N/A	betaxolol
Bisoprolol	tablet	N/A	bisoprolol
Carvedilol	extended-release capsule, tablet	Coreg®*, Coreg CR®*	carvedilol
Esmolol	injection^	Brevibloc®*	none
Labetalol	injection^, tablet	N/A	labetalol
Metoprolol	extended-release capsule, extended-release tablet, injection, tablet	Kapspargo Sprinkle®, Lopressor®*, Toprol-XL®*	metoprolol
Nadolol	tablet	N/A	nadolol
Nebivolol	tablet	Bystolic®*	Bystolic®*, nebivolol
Penbutolol	tablet	Levatol®†	none
Pindolol	tablet	N/A	pindolol
Propranolol	extended-release capsule, injection, solution, tablet	Hemangeol®, Inderal LA®*, Inderal XL®, InnoPran XL®	Hemangeol®CC, propranolol
Sotalol	tablet, solution	Betapace®*, Betapace	sotalol

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
		AF®*, Sotylize®	
Timolol	tablet	N/A	timolol
Combination Products			
Atenolol and chlorthalidone	tablet	Tenoretic®*	atenolol and chlorthalidone
Bisoprolol and hydrochlorothiazide	tablet	Ziac®*	bisoprolol and hydrochlorothiazide
Metoprolol and hydrochlorothiazide	tablet	N/A	metoprolol and hydrochlorothiazide
Nadolol and bendroflumethiazide	tablet	N/A	nadolol and bendroflumethiazide

*Generic is available in at least one dosage form or strength.
^Product is primarily administered in an institution.
†Product was discontinued by manufacturer, but remains active in pharmacy system.
PDL=Preferred Drug List
N/A=Not available

Table 2. Selected Pharmacologic Properties of the Beta-Adrenergic Blocking Agents[1-3]

Generic Name(s)	Adrenergic-Receptor Blocking Activity	Membrane Stabilizing Activity	Intrinsic Sympathomimetic Activity
Acebutolol	β_1*	+†	+
Atenolol	β_1*	0	0
Betaxolol	β_1*	+	0
Bisoprolol	β_1*	0	0
Carvedilol	α_1 - β_1 - β_2	++	0
Labetalol	α_1 - β_1 - β_2	0	+
Metoprolol	β_1*	0†	0
Nadolol	β_1 - β_2	0	0
Nebivolol	β_1*	0	0
Penbutolol	β_1 - β_2	0	+
Pindolol	β_1 - β_2	+	++
Propranolol	β_1 - β_2	++	0
Sotalol	β_1 - β_2	0	0
Timolol	β_1 - β_2	0	0

0=none; +=low; ++=moderate; +++ =high
*Inhibits β_2 receptors (bronchial and vascular) at higher doses.
†Detectable only at doses much greater than required for β blockade.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the β-adrenergic blocking agents are summarized in Table 3.

Table 3. Treatment Guidelines Using the Beta-Adrenergic Blocking Agents

Clinical Guideline	Recommendations
European Society of Cardiology: **Guidelines for the Diagnosis and Management of Chronic Coronary Syndromes (2019)[7]**	<u>Pharmacological management of stable coronary artery disease (CAD) patients</u> • The two aims of the pharmacological management of stable CAD patients are to obtain relief of symptoms and to prevent CV events. • Optimal medical treatment indicates at least one drug for angina/ischaemia relief plus drugs for event prevention. • It is recommended to educate patients about the disease, risk factors and treatment strategy. • It is indicated to review the patient's response soon after starting therapy.

Clinical Guideline	Recommendations
	• Concomitant use of a proton pump inhibitor is recommended in patients receiving aspirin monotherapy, DAPT, or DOAC monotherapy who are at high risk of gastrointestinal bleeding. • Lipid-lowering drugs: if goals are not met on maximum tolerated dose of a statin, consideration of combination therapy with ezetimibe or a PCSK9 inhibitor is recommended • ACE inhibitors should be considered in patients at a very high risk of cardiovascular adverse events • Angina/ischemia relief: o Short-acting nitrates are recommended. o First-line treatment is indicated with ß-blockers and/or calcium channel blockers to control heart rate and symptoms. o Long-acting nitrates should be considered as a second-line treatment option when initial therapy with a beta-blocker and/or a non-DHP-calcium channel blocker is contraindicated, poorly tolerated, or inadequate in controlling angina symptoms o Nicorandil, ranolazine, ivabradine, or trimetazidine should be considered as a second-line treatment to reduce angina frequency and improve exercise tolerance in subjects who cannot tolerate, have contraindications to, or whose symptoms are not adequately controlled by beta-blockers, CCBs, and long-acting nitrates. o According to comorbidities/tolerance, it is indicated to use second-line therapies as first-line treatment in selected patients. o In asymptomatic patients with large areas of ischaemia (>10%) ß-blockers should be considered. o In patients with vasospastic angina, calcium channel blockers and nitrates should be considered and beta-blockers avoided. • Event prevention: o Low-dose aspirin daily is recommended in all stable CAD patients. o Clopidogrel is indicated as an alternative in case of aspirin intolerance. o Statins are recommended in all stable CAD patients. o It is recommended to use ACE inhibitors (or ARBs) if presence of other conditions (e.g., heart failure, hypertension or diabetes). <u>Treatment in patients with microvascular angina</u> • It is recommended that all patients receive secondary prevention medications including aspirin and statins. • ß-blockers are recommended as a first-line treatment. • Calcium antagonists are recommended if ß-blockers do not achieve sufficient symptomatic benefit or are not tolerated. • ACE inhibitors or nicorandil may be considered in patients with refractory symptoms. • Xanthine derivatives or nonpharmacological treatments such as neurostimulatory techniques may be considered in patients with symptoms refractory to the above listed drugs. <u>Stenting and peri-procedural antiplatelet strategies in stable CAD patients</u> • Drug-eluting stent (DES) is recommended in stable CAD patients undergoing stenting if there is no contraindication to prolonged dual antiplatelet therapy (DAPT). • Aspirin is recommended for elective stenting. • Clopidogrel is recommended for elective stenting. • Prasugrel or ticagrelor should be considered in patients with stent thrombosis on clopidogrel without treatment interruption. • GP IIb/IIIa antagonists should be considered for bailout situation only.

Clinical Guideline	Recommendations
	• Platelet function testing or genetic testing may be considered in specific or high risk situations (e.g., prior history of stent thrombosis; compliance issue; suspicion of resistance; high bleeding risk) if results may change the treatment strategy. • Prasugrel or ticagrelor may be considered in specific high-risk situations of elective stenting (e.g., left main stenting, high risk of stent thrombosis, diabetes). • Pretreatment with clopidogrel (when coronary anatomy is not known) is not recommended. • Routine platelet function testing (clopidogrel and aspirin) to adjust antiplatelet therapy before or after elective stenting is not recommended. • Prasugrel or ticagrelor is not recommended in low-risk elective stenting. • After uncomplicated PCI, early cessation (≤1 week) of aspirin, and continuation of dual therapy with oral anticoagulation therapy and clopidogrel should be considered if the risk of stent thrombosis is low • Triple therapy with aspirin, clopidogrel, and a DOAC for ≥1 month should be considered when the risk of stent thrombosis outweighs the bleeding risk, with a total of no more than six months <u>Follow-up of revascularized stable coronary artery disease patients</u> • It is recommended that all revascularized patients receive a secondary prevention and be scheduled for follow-up visit. • It is recommended to instruct patients before discharge about return to work and reuptake of full activities. Patients have to be advised to seek immediate medical contact if symptoms (re-) occur. • Single antiplatelet therapy, usually aspirin, is recommended indefinitely. • DAPT is indicated after bare metal stent (BMS) for at least one month. • DAPT is indicated for six to 12 months after second generation DES. • DAPT may be used for more than one year in patients at high ischemic risk (e.g., stent thrombosis, recurrent acute coronary syndrome on DAPT, post MI/diffuse CAD) and low bleeding risk. • DAPT for one to three months may be used after DES implantation in patients at high bleeding risk or with undeferrable surgery or concomitant anticoagulant treatment. <u>Antithrombotic therapy in patients with chronic coronary syndrome:</u> • Addition of a second antithrombotic drug to aspirin for long-term secondary prevention should be considered in patients with at least a moderately increased risk of ischemic events and without high bleeding risk • When oral anticoagulation is initiated in patients with AF, a DOAC is recommended in preference to VKA therapy.
American Heart Association/American College of Cardiology/American College of Clinical Pharmacy/American Society for Preventive Cardiology/National Lipid Association/ Preventive Cardiovascular Nurses Association **Guideline for the Management of Patients With**	• In patients with chronic coronary disease (CCD), high-intensity statin therapy is recommended with the aim of achieving a ≥50% reduction in LDL-C levels to reduce the risk of major adverse cardiovascular events (MACE). • In patients in whom high-intensity statin therapy is contraindicated or not tolerated, moderate-intensity statin therapy is recommended with the aim of achieving a 30% to 49% reduction in LDL-C levels to reduce the risk of MACE. • In patients with CCD who are judged to be at very high risk and on maximally tolerated statin therapy with an LDL-C level ≥70 mg/dL, ezetimibe can be beneficial to further reduce the risk of MACE. • In patients with CCD who are judged to be at very high risk and who have an LDL-C level ≥70 mg/dL, or a non–high-density lipoprotein cholesterol (HDL-C) level ≥100 mg/dL, on maximally tolerated statin and ezetimibe, a PCSK9 monoclonal antibody can be beneficial to further reduce the risk of MACE. • In patients with CCD on maximally tolerated statin therapy with an LDL-C level <100 mg/dL and a persistent fasting triglyceride level of 150 to 499 mg/dL after addressing secondary causes, icosapent ethyl may be considered to further reduce

Clinical Guideline	Recommendations
Chronic Coronary Disease (2023)[8]	the risk of MACE and cardiovascular death. • In patients with CCD who are not at very high risk and on maximally tolerated statin therapy with an LDL-C level ≥70 mg/dL, it may be reasonable to add ezetimibe to further reduce the risk of MACE. • In patients with CCD on maximally tolerated statin therapy who have an LDL-C level ≥70 mg/dL, and in whom ezetimibe and PCSK9 monoclonal antibody are deemed insufficient or not tolerated, it may be reasonable to add bempedoic acid or inclisiran (in place of PCSK9 monoclonal antibody) to further reduce LDL-C levels. • In patients with CCD receiving statin therapy, adding niacin, fenofibrate, or dietary supplements containing omega-3 fatty acids are not beneficial in reducing cardiovascular risk. • In adults with CCD, nonpharmacologic strategies are recommended as first-line therapy to lower BP in those with elevated BP (120-129/<80 mmHg). • In adults with CCD who have hypertension, a BP target of <130/<80 mmHg is recommended to reduce CVD events and all-cause death. • In adults with CCD and hypertension (systolic BP ≥130 and/or diastolic BP ≥80 mm Hg), in addition to nonpharmacological strategies, GDMT angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), or beta blockers are recommended as first-line therapy for compelling indications (e.g., recent MI or angina), with additional antihypertensive medications (e.g., dihydropyridine calcium channel blockers [CCB], long-acting thiazide diuretics, and/or mineralocorticoid receptor antagonists) added as needed to optimize BP control. • In patients with CCD and no indication for oral anticoagulant therapy, low-dose aspirin 81 mg (75 to 100 mg) is recommended to reduce atherosclerotic events. • In patients with CCD treated with PCI, dual antiplatelet therapy (DAPT) consisting of aspirin and clopidogrel for 6 months post PCI followed by single antiplatelet therapy (SAPT) is indicated to reduce MACE and bleeding events.* • In select patients with CCD treated with PCI and a drug-eluting stent (DES) who have completed a 1- to 3-month course of DAPT, P2Y12 inhibitor monotherapy for at least 12 months is reasonable to reduce bleeding risk. • In patients with CCD who have had a previous MI and are at low bleeding risk, extended DAPT beyond 12 months for a period of up to three years may be reasonable to reduce MACE. • In patients with CCD and a previous history of MI without a history of stroke, transient ischemic attack (TIA), or ICH, vorapaxar may be added to aspirin therapy to reduce MACE. • In patients with CCD, the use of DAPT after CABG may be useful to reduce the incidence of saphenous vein graft occlusion. • In patients with CCD without recent ACS or a PCI-related indication for DAPT, the addition of clopidogrel to aspirin therapy is not useful to reduce MACE. • In patients with CCD and previous stroke, TIA, or ICH, vorapaxar should not be added to DAPT because of increased risk of major bleeding and ICH. • In patients with CCD and previous stroke, TIA, or ICH, prasugrel should not be used because of risk of significant or fatal bleeding. • In patients with CCD, chronic nonsteroidal anti-inflammatory drugs should not be used because of increased cardiovascular and bleeding complications. • In patients with CCD who have undergone elective PCI and who require oral anticoagulant therapy, DAPT for one to four weeks followed by clopidogrel alone for six months should be administered in addition to DOAC. • In patients with CCD who have undergone PCI and who require oral anticoagulant therapy, continuing aspirin in addition to clopidogrel for up to 1 month is reasonable if the patient has a high thrombotic risk and low bleeding risk. • In patients with CCD who require oral anticoagulation and have a low

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	atherothrombotic risk, discontinuation of aspirin therapy with continuation of DOAC alone may be considered one year after PCI to reduce bleeding risk. • In patients with CCD who require oral anticoagulation, DOAC monotherapy may be considered if there is no acute indication for concomitant antiplatelet therapy. • In patients with CCD without an indication for therapeutic DOAC or DAPT and who are at high risk of recurrent ischemic events but low-to-moderate bleeding risk, the addition of low-dose rivaroxaban 2.5 mg twice daily to aspirin 81 mg daily is reasonable for long-term reduction of risk for MACE. • In patients with CCD on DAPT, the use of a PPI can be effective in reducing gastrointestinal bleeding risk. • In patients with CCD and LVEF ≤40% with or without previous MI, the use of beta-blocker therapy is recommended to reduce the risk of future MACE, including cardiovascular death. • In patients with CCD and LVEF<50%, the use of sustained release metoprolol succinate, carvedilol, or bisoprolol with titration to target doses is recommended in preference to other beta blockers. • In patients with CCD who were initiated on beta-blocker therapy for previous MI without a history of or current LVEF ≤50%, angina, arrhythmias, or uncontrolled hypertension, it may be reasonable to reassess the indication for long-term (>1 year) use of beta-blocker therapy for reducing MACE. • In patients with CCD without previous MI or LVEF ≤50%, the use of beta-blocker therapy is not beneficial in reducing MACE, in the absence of another primary indication for beta-blocker therapy. • In patients with CCD who also have hypertension, diabetes, LVEF ≤40%, or CKD, the use of ACE inhibitors, or ARBs if ACE inhibitor–intolerant, is recommended to reduce cardiovascular events. • In patients with CCD without hypertension, diabetes, or CKD and LVEF >40%, the use of ACE inhibitors or ARBs may be considered to reduce cardiovascular events. • In patients with CCD, the addition of colchicine for secondary prevention may be considered to reduce recurrent ASCVD events. • In patients with CCD, an annual influenza vaccination is recommended to reduce cardiovascular morbidity, cardiovascular death, and all-cause death. • In patients with CCD, coronavirus disease 2019 (COVID-19) vaccination is recommended per public health guidelines to reduce COVID-19 complications. • In patients with CCD, a pneumococcal vaccine is reasonable to reduce cardiovascular morbidity and mortality and all-cause death. • In patients with CCD and angina, antianginal therapy with either a beta blocker, CCB, or long-acting nitrate is recommended for relief of angina or equivalent symptoms. • In patients with CCD and angina who remain symptomatic after initial treatment, addition of a second antianginal agent from a different therapeutic class (beta blockers, CCB, long-acting nitrates) is recommended for relief of angina or equivalent symptoms. • In patients with CCD, ranolazine is recommended in patients who remain symptomatic despite treatment with beta blockers, CCB, or long-acting nitrate therapies. • In patients with CCD, sublingual nitroglycerin or nitroglycerin spray is recommended for immediate short-term relief of angina or equivalent symptoms. • In patients with CCD and normal LV function, the addition of ivabradine to standard anti-anginal therapy is potentially harmful. • In patients with CCD and lifestyle-limiting angina despite GDMT and with significant coronary artery stenoses amenable to revascularization, revascularization is recommended to improve symptoms. • In patients with CCD who have experienced SCAD, beta-blocker therapy may be

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	reasonable to reduce the incidence of recurrent SCAD. • Women with CCD who are contemplating pregnancy or who are pregnant should not use ACE inhibitors, ARBs, direct renin inhibitors, angiotensin receptor-neprilysin inhibitors, or aldosterone antagonists during pregnancy to prevent harm to the fetus. • Women with CCD should not receive systemic postmenopausal hormone therapy because of a lack of benefit on MACE and mortality, and an increased risk of venous thromboembolism.

European Society of Cardiology: **Guidelines for the Diagnosis and Management of Chronic Coronary Syndromes (2019)[9]**	<u>Pharmacological management of stable coronary artery disease (CAD) patients</u>
	• The two aims of the pharmacological management of stable CAD patients are to obtain relief of symptoms and to prevent CV events.
	• Optimal medical treatment indicates at least one drug for angina/ischaemia relief plus drugs for event prevention.
	• It is recommended to educate patients about the disease, risk factors and treatment strategy.
	• It is indicated to review the patient's response soon after starting therapy.
	• Concomitant use of a proton pump inhibitor is recommended in patients receiving aspirin monotherapy, DAPT, or DOAC monotherapy who are at high risk of gastrointestinal bleeding.
	• Lipid-lowering drugs: if goals are not met on maximum tolerated dose of a statin, consideration of combination therapy with ezetimibe or a PCSK9 inhibitor is recommended
	• ACE inhibitors should be considered in patients at a very high risk of cardiovascular adverse events
	• Angina/ischemia relief:
	  ○ Short-acting nitrates are recommended.
	  ○ First-line treatment is indicated with ß-blockers and/or calcium channel blockers to control heart rate and symptoms.
	  ○ Long-acting nitrates should be considered as a second-line treatment option when initial therapy with a beta-blocker and/or a non-DHP-calcium channel blocker is contraindicated, poorly tolerated, or inadequate in controlling angina symptoms
	  ○ Nicorandil, ranolazine, ivabradine, or trimetazidine should be considered as a second-line treatment to reduce angina frequency and improve exercise tolerance in subjects who cannot tolerate, have contraindications to, or whose symptoms are not adequately controlled by beta-blockers, CCBs, and long-acting nitrates.
	  ○ According to comorbidities/tolerance, it is indicated to use second-line therapies as first-line treatment in selected patients.
	  ○ In asymptomatic patients with large areas of ischaemia (>10%) ß-blockers should be considered.
	  ○ In patients with vasospastic angina, calcium channel blockers and nitrates should be considered and beta-blockers avoided.
	• Event prevention:
	  ○ Low-dose aspirin daily is recommended in all stable CAD patients.
	  ○ Clopidogrel is indicated as an alternative in case of aspirin intolerance.
	  ○ Statins are recommended in all stable CAD patients.
	  ○ It is recommended to use ACE inhibitors (or ARBs) if presence of other conditions (e.g., heart failure, hypertension or diabetes).
	
	<u>Treatment in patients with microvascular angina</u>
	• It is recommended that all patients receive secondary prevention medications including aspirin and statins.
	• ß-blockers are recommended as a first-line treatment.
	• Calcium antagonists are recommended if ß-blockers do not achieve sufficient

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	symptomatic benefit or are not tolerated. • ACE inhibitors or nicorandil may be considered in patients with refractory symptoms. • Xanthine derivatives or nonpharmacological treatments such as neurostimulatory techniques may be considered in patients with symptoms refractory to the above listed drugs. <u>Stenting and peri-procedural antiplatelet strategies in stable CAD patients</u> • Drug-eluting stent (DES) is recommended in stable CAD patients undergoing stenting if there is no contraindication to prolonged dual antiplatelet therapy (DAPT). • Aspirin is recommended for elective stenting. • Clopidogrel is recommended for elective stenting. • Prasugrel or ticagrelor should be considered in patients with stent thrombosis on clopidogrel without treatment interruption. • GP IIb/IIIa antagonists should be considered for bailout situation only. • Platelet function testing or genetic testing may be considered in specific or high-risk situations (e.g., prior history of stent thrombosis; compliance issue; suspicion of resistance; high bleeding risk) if results may change the treatment strategy. • Prasugrel or ticagrelor may be considered in specific high-risk situations of elective stenting (e.g., left main stenting, high risk of stent thrombosis, diabetes). • Pretreatment with clopidogrel (when coronary anatomy is not known) is not recommended. • Routine platelet function testing (clopidogrel and aspirin) to adjust antiplatelet therapy before or after elective stenting is not recommended. • Prasugrel or ticagrelor is not recommended in low-risk elective stenting. • After uncomplicated PCI, early cessation (≤1 week) of aspirin, and continuation of dual therapy with oral anticoagulation therapy and clopidogrel should be considered if the risk of stent thrombosis is low. • Triple therapy with aspirin, clopidogrel, and a DOAC for ≥1 month should be considered when the risk of stent thrombosis outweighs the bleeding risk, with a total of no more than six months. <u>Follow-up of revascularized stable coronary artery disease patients</u> • It is recommended that all revascularized patients receive a secondary prevention and be scheduled for follow-up visit. • It is recommended to instruct patients before discharge about return to work and reuptake of full activities. Patients have to be advised to seek immediate medical contact if symptoms (re-) occur. • Single antiplatelet therapy, usually aspirin, is recommended indefinitely. • DAPT is indicated after bare metal stent (BMS) for at least one month. • DAPT is indicated for six to 12 months after second generation DES. • DAPT may be used for more than one year in patients at high ischemic risk (e.g., stent thrombosis, recurrent acute coronary syndrome on DAPT, post MI/diffuse CAD) and low bleeding risk. • DAPT for one to three months may be used after DES implantation in patients at high bleeding risk or with undeferrable surgery or concomitant anticoagulant treatment. <u>Antithrombotic therapy in patients with chronic coronary syndrome:</u> • Addition of a second antithrombotic drug to aspirin for long-term secondary prevention should be considered in patients with at least a moderately increased risk of ischemic events and without high bleeding risk. • When oral anticoagulation is initiated in patients with AF, a DOAC is recommended in preference to VKA therapy.

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American College of Cardiology Foundation/ American Heart Association: **2014 American Heart Association/ American College of Cardiology Foundation Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes (2014)[10]**	Early hospital care- standard medical therapies • Supplemental oxygen should be administered to patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) with arterial oxygen saturation <90%, respiratory distress, or other high risk features of hypoxemia. • Anti-ischemic and analgesic medications o Nitrates ▪ Patients with NSTE-ACS with continuing ischemic pain should receive sublingual nitroglycerin (0.3 to 0.4 mg) every 5 minutes for up to three doses, after which an assessment should be made about the need for intravenous nitroglycerin. ▪ Intravenous nitroglycerin is indicated for patients with NSTE-ACS for the treatment of persistent ischemia, heart failure, or hypertension. ▪ Nitrates should not be administered to patients who recently received a phosphodiesterase inhibitor, especially within 24 hours of sildenafil or vardenafil, or within 48 hours of tadalafil. o Analgesic therapy ▪ In the absence of contraindications, it may be reasonable to administer morphine sulphate intravenously to patients with NSTE-ACE if there is continued ischemic chest pain despite treatment with maximally tolerated anti-ischemic medications. ▪ Nonsteroidal anti-inflammatory drugs (NSAIDs) (except aspirin) should not be initiated and should be discontinued during hospitalization due to the increased risk of major adverse cardiac event associated with their use o Beta-adrenergic blockers ▪ Oral β-blocker therapy should be initiated within the first 24 hours in patients who do not have any of the following: 1) signs of HF, 2) evidence of low-output state, 3) increased risk for cardiogenic shock, or 4) other contraindications to βblockade (e.g., PR interval >0.24 second, second- or third-degree heart block without a cardiac pacemaker, active asthma, or reactive airway disease) ▪ In patients with concomitant NSTE-ACS, stabilized heart failure, and reduced systolic function, it is recommended to continue β-blocker therapy with one of the three drugs proven to reduce mortality in patients with heart failure: sustained-release metoprolol succinate, carvedilol, or bisoprolol. ▪ Patients with documented contraindications to β-blockers in the first 24 hours should be re-evaluated to determine subsequent eligibility. o Calcium channel blockers (CCBs) ▪ In patients with NSTE-ACS, continuing or frequently recurring ischemia, and a contraindication to β-blockers, a nondihydropyridine CCB (e.g., verapamil or diltiazem) should be given as initial therapy in the absence of clinically significant LV dysfunction, increased risk for cardiogenic shock, PR interval >0.24 seconds, or second or third degree atrioventricular block without a cardiac pacemaker. ▪ Oral nondihydropyridine calcium antagonists are recommended in patients with NSTE-ACS who have recurrent ischemia in the absence of contraindications, after appropriate use of β-blockers and nitrates. ▪ CCBs are recommended for ischemic symptoms when β-blockers are not successful, are contraindicated, or cause unacceptable side effects. ▪ Long-acting CCBs and nitrates are recommended in patients with coronary artery spasm. ▪ Immediate-release nifedipine should not be administered to patients with NSTE-ACS in the absence of β-blocker therapy. o Other anti-ischemic interventions ▪ Ranolazine is currently indicated for treatment of chronic angina;

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	however, it may also improve outcomes in NSTE-ACS patients due to a reduction in recurrent ischemia. o Cholesterol management ▪ High-intensity statin therapy should be initiated or continued in all patients with NSTE-ACS and no contraindications to its use. Treatment with statins reduces the rate of recurrent MI, coronary heart disease mortality, need for myocardial revascularization, and stroke. ▪ It is reasonable to obtain a fasting lipid profile in patients with NSTE-ACS, preferably within 24 hours of presentation. • Inhibitors of renin-angiotensin-aldosterone system o ACE inhibitors should be started and continued indefinitely in all patients with LVEF <0.40 and in those with hypertension, diabetes mellitus, or stable CKD, unless contraindicated. o ARBs are recommended in patients with heart failure or myocardial infarction with LVEF <0.40 who are ACE inhibitor intolerant. o Aldosterone-blockade is recommended in patients post-MI without significant renal dysfunction (creatinine >2.5 mg/dL in men or >2.0 mg/dL in women) or hyperkalemia (K >5.0 mEq/L) who are receiving therapeutic doses of ACE inhibitor and β-blocker and have a LVEF <0.40, diabetes mellitus, or heart failure. • Initial antiplatelet/anticoagulant therapy in patients with definite or likely NSTE-ACS treated with an initial invasive or ischemia-guided strategy o Non-enteric coated, chewable aspirin (162 to 325 mg) should be given to all patients with NSTE-ACS without contraindications as soon as possible after presentation, and a maintenance dose of aspirin (81 to 162 mg/day) should be continued indefinitely. o In patients who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance, a loading dose of clopidogrel followed by a daily maintenance dose should be administered. o A $P2Y_{12}$ receptor inhibitor (clopidogrel or ticagrelor) in addition to aspirin should be administered for up to 12 months to all patients with NSTE-ACS without contraindications who are treated with an early invasive or ischemia-guided strategy. Options include: ▪ Clopidogrel: 300 or 600 mg loading dose, then 75 mg daily. ▪ Ticagrelor: 180 mg loading dose, then 90 mg twice daily. ▪ It is reasonable to use ticagrelor in preference to clopidogrel for $P2Y_{12}$ treatment in patients with NSTE-ACS who undergo an early invasive or ischemia-guided strategy. ▪ In patients with NSTE-ACS treated with an early invasive strategy and dual antiplatelet therapy (DAPT) with intermediate/high-risk features (e.g., positive troponin), a GP IIb/IIIa inhibitor may be considered as part of initial antiplatelet therapy. Preferred options are eptifibatide or tirofiban. <u>Percutaneous coronary intervention (PCI)- Antiplatelet and anticoagulant therapy</u> • Antiplatelet agents o Patients already taking daily aspirin before PCI should take 81 to 325 mg non-enteric coated aspirin before PCI o Patients not on aspirin therapy should be given non-enteric coated aspirin 325 mg as soon as possible before PCI. o After PCI, aspirin should be continued indefinitely. o A loading dose of a $P2Y_{12}$ inhibitor should be given before the procedure in patients undergoing PCI with stenting. Options include clopidogrel 600 mg, prasugrel 60 mg, or ticagrelor 180 mg. o In patients with NSTE-ACS and high-risk features (e.g., elevated troponin) not adequately pretreated with clopidogrel or ticagrelor, it is useful to

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	administer a GP IIb/IIIa inhibitor (abciximab, double-bolus eptifibatide, or high-dose bolus tirofiban) at the time of PCI. o In patients receiving a stent (bare metal or drug eluting) during PCI, $P2Y_{12}$ inhibitor therapy should be given for at least 12 months. Options include clopidogrel 75 mg daily, prasugrel 10 mg daily, or ticagrelor 90 mg twice daily. • Anticoagulant therapy o An anticoagulant should be administered to patients with NSTE-ACS undergoing PCI to reduce the risk of intracoronary and catheter thrombus formation. o Intravenous unfractionated heparin (UFH) is useful in patients with NSTE-ACS undergoing PCI. o Bivalirudin is useful as an anticoagulant with or without prior treatment with UFH. o An additional dose of 0.3 mg/kg intravenous enoxaparin should be administered at the time of PCI to patients with NSTE-ACS who have received fewer than two therapeutic subcutaneous doses or received the last subcutaneous enoxaparin dose eight to 12 hours before PCI. o If PCI is performed while the patient is on fondaparinux, an additional 85 IU/kg of UFH should be given intravenously immediately before PCI because of the risk of catheter thrombosis (60 IU/kg IV if a GP IIb/IIIa inhibitor used with UFH dosing based on the target-activated clotting time). o Anticoagulant therapy should be discontinued after PCI unless there is a compelling reason to continue. • Timing of coronary artery bypass grafting (CABG) in relation to use of antiplatelet agents o Non-enteric coated aspirin (81 to 325 mg daily) should be administered preoperatively to patients undergoing CABG. o In patients referred for elective CABG, clopidogrel and ticagrelor should be discontinued for at least five days before surgery and prasugrel for at least seven days before surgery. o In patients referred for urgent CABG, clopidogrel and ticagrelor should be discontinued for at least 24 hours to reduce major bleeding. o In patients referred for CABG, short-acting intravenous GP IIb/IIIa inhibitors (eptifibatide or tirofiban) should be discontinued for at least 2 to 4 hours before surgery and abciximab for at least 12 hours before to limit blood loss and transfusion. <u>Late hospital care, hospital discharge, and posthospital discharge care</u> • Medications at discharge o Medications required in the hospital to control ischemia should be continued after hospital discharge in patients with NSTE-ACS who do not undergo coronary revascularization, patients with incomplete or unsuccessful revascularization, and patients with recurrent symptoms after revascularization. Titration of the doses may be required. o All patients who are post–NSTE-ACS should be given sublingual or spray nitroglycerin with verbal and written instructions for its use. o Before hospital discharge, patients with NSTE-ACS should be informed about symptoms of worsening myocardial ischemia and MI and should be given verbal and written instructions about how and when to seek emergency care for such symptoms. o Before hospital discharge, patients who are post–NSTE-ACS and/or designated responsible caregivers should be provided with easily understood and culturally sensitive verbal and written instructions about medication type, purpose, dose, frequency, side effects, and duration of use. o For patients who are post–NSTE-ACS and have initial angina lasting more

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	than one minute, nitroglycerin (one dose sublingual or spray) is recommended if angina does not subside within three to five minutes; call 9-1-1 immediately to access emergency medical services. o If the pattern or severity of angina changes, suggesting worsening myocardial ischemia (e.g., pain is more frequent or severe or is precipitated by less effort or occurs at rest), patients should contact their clinician without delay to assess the need for additional treatment or testing. o Before discharge, patients should be educated about modification of cardiovascular risk factors. • Late hospital and post-hospital oral antiplatelet therapy o Aspirin should be continued indefinitely. The dose should be 81 mg daily in patients treated with ticagrelor and 81 to 325 mg daily in all other patients. o In addition to aspirin, a $P2Y_{12}$ inhibitor (either clopidogrel or ticagrelor) should be continued for up to 12 months in all patients with NSTE-ACS without contraindications who are treated with an ischemia-guided strategy. o In patients receiving a stent (bare-metal stent or DES) during PCI for NSTE-ACS, $P2Y_{12}$ inhibitor therapy should be given for at least 12 months. • Combined oral anticoagulant therapy and antiplatelet therapy in patients with NSTE-ACS o The duration of triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a $P2Y_{12}$ receptor inhibitor in patients with NSTE-ACS should be minimized to the extent possible to limit the risk of bleeding. o Proton pump inhibitors should be prescribed in patients with NSTE-ACS with a history of gastrointestinal bleeding who require triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a $P2Y_{12}$ receptor inhibitor.
American College of Cardiology/ American Heart Association: **Guideline for the Management of ST-Elevation Myocardial Infarction (2013)[11]**	<u>Routine medical therapies: β-blockers</u> • Oral β-blockers should be initiated within the first 24 hours in patients with an ST-segment elevation myocardial infarction (STEMI) who do not have any of the following: 1) signs of heart failure, 2) evidence of a low-output state, 3) increased risk of cardiogenic shock, 4) other contraindications to use of oral β-blockers (e.g., PR interval >24 seconds, second or third degree heart block, active asthma, reactive airway disease). • β-blockers should be continued during and after hospitalization for all patients with STEMI and with no contraindications to their use. • Patients with initial contraindications to the use of β-blockers in the first 24 hours after STEMI should be re-evaluated to determine their subsequent eligibility. • It is reasonable to administer intravenous β-blockers at the time of presentation to patients with STEMI and no contraindications to their use who are hypertensive or have ongoing ischemia. <u>Routine medical therapies: Renin-Angiotensin-Aldosterone System Inhibitors</u> • An angiotensin-converting enzyme (ACE) inhibitor should be administered within the first 24 hours to all patients with STEMI with anterior location, HF, or ejection fraction (EF) ≤40%, unless contraindicated. • An angiotensin receptor blocker (ARB) should be given to patients with STEMI who have indications for but are intolerant of ACE inhibitors. • An aldosterone antagonist should be given to patients with STEMI and no contraindications who are already receiving an ACE inhibitor and β-blocker and who have an EF ≤40% and either symptomatic heart failure or diabetes. <u>Routine medical therapies: Lipid management</u> • High-intensity statin therapy should be initiated or continued in all patients with STEMI and no contraindications to its use. • It is reasonable to obtain a fasting lipid profile in patients with STEMI, preferably within 24 hours of presentation.

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European Society of Cardiology: **Management of Acute Myocardial Infarction in Patients Presenting with ST-segment Elevation (2017)**[12]	Routine therapies in the acute, subacute and long term phase of STEMI • Antiplatelet therapy with low dose aspirin (75 to 100 mg) is indicated indefinitely after STEMI. • Dual antiplatelet therapy with a combination of aspirin and prasugrel or aspirin and ticagrelor is recommended for 12 months after percutaneous coronary intervention (PCI), unless there are contraindications such as excessive risk of bleeding. • A proton pump inhibitor (PPI) in combination with dual antiplatelet therapy is recommended in patients at high risk of gastrointestinal bleeding. • In patients with an indication for oral anticoagulation, oral anticoagulants are indicated in addition to antiplatelet therapy • In patients who are at high risk of severe bleeding complications, discontinuation of $P2Y_{12}$ inhibitor therapy after six months should be considered. • In STEMI patients with stent implantation and an indication for oral anticoagulation, triple therapy (oral anticoagulant, aspirin, and clopidogrel) should be considered for one to six months (according a balance between the estimated risk of recurrent coronary events and bleeding). • In patients with left ventricular thrombus, anticoagulation should be instituted for a minimum of six months, guided by repeated imaging. • In selected patients who receive aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily) may be considered if the patient is at low bleeding risk. • Dual antiplatelet therapy should be used up to one year in patients with STEMI who did not receive a stent unless there are contraindications such as excessive risk of bleeding. • In high ischemic-risk patients (age ≥50 years, and at least one of the following risk factors: age ≥65 years, diabetes mellitus on medication, prior spontaneous MAI, multivessel CAD, or chronic renal dysfunction with eGFR <60 mL/min) who have tolerated dual antiplatelet therapy without a bleeding complication, treatment with dual antiplatelet therapy in the form of ticagrelor 60 mg twice a day on top of aspirin for longer than 12 months may be considered for up to three years. • The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with aspirin and oral anticoagulation. • Oral treatment with β-blockers should be considered during hospital stay and continued thereafter in all patients without contraindications. • Oral treatment with β-blockers is indicated in patients with heart failure or left ventricular dysfunction, LVEF <40% unless contraindicated. • Intravenous β-blockers must be avoided in patients with hypotension or acute heart failure or AV block or severe bradycardia. • Intravenous β-blockers should be considered at the time of presentation in patients undergoing primary PCI without contraindications, with high blood pressure, tachycardia, and no signs of heart failure. • A fasting lipid profile must be obtained in all STEMI patients, as soon as possible after presentation. • It is recommended to initiate or continue high dose statins early after admission in all STEMI patients without contraindication or history of intolerance, regardless of initial cholesterol values and maintain it long-term. • An LDL-C goal of <1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline LDL-C is between 1.8 to 3.5 mmol/L (70 to 135 mg/dL) is recommended. • In patients with LDL-C >1.8 mmol/L (>70 mg/dL) despite a maximally tolerated statin dose who remain at high risk, further therapy to reduce LDL-C should be considered. • ACE inhibitors are indicated starting within the first 24 hours of STEMI in patients with evidence of heart failure, LV systolic dysfunction, diabetes or an

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	anterior infarct. • An ARB, preferably valsartan, is an alternative to ACE inhibitors in patients with heart failure or LV systolic dysfunction, particularly those who are intolerant to ACE inhibitors. • ACE inhibitors should be considered in all patients in the absence of contraindications. • Aldosterone antagonists, e.g. eplerenone, are indicated in patients with an ejection fraction ≤40% and heart failure or diabetes, provided no renal failure or hyperkalemia.
American college of Cardiology/ American Heart Association: **Guideline on the Primary Prevention of Cardiovascular disease (2019)**[13]	<u>Top 10 messages for the primary prevention of cardiovascular disease</u> • The most important way to prevent atherosclerotic vascular disease, heart failure, and atrial fibrillation is to promote a healthy lifestyle throughout life. • A team-based care approach is an effective strategy for the prevention of cardiovascular disease. Clinicians should evaluate the social determinants of health that affect individuals to inform treatment decisions. • Adults who are 40 to 75 years of age and are being evaluated for cardiovascular disease prevention should undergo 10-year atherosclerotic cardiovascular disease (ASCVD) risk estimation and have a clinician–patient risk discussion before starting on pharmacological therapy, such as antihypertensive therapy, a statin, or aspirin. In addition, assessing for other risk-enhancing factors can help guide decisions about preventive interventions in select individuals, as can coronary artery calcium scanning. • All adults should consume a healthy diet that emphasizes the intake of vegetables, fruits, nuts, whole grains, lean vegetable or animal protein, and fish and minimizes the intake of trans fats, processed meats, refined carbohydrates, and sweetened beverages. For adults with overweight and obesity, counseling and caloric restriction are recommended for achieving and maintaining weight loss. • Adults should engage in at least 150 minutes per week of accumulated moderate-intensity physical activity or 75 minutes per week of vigorous-intensity physical activity. • For adults with type 2 diabetes mellitus, lifestyle changes, such as improving dietary habits and achieving exercise recommendations, are crucial. If medication is indicated, metformin is first-line therapy, followed by consideration of a sodium-glucose cotransporter 2 inhibitor or a glucagon-like peptide-1 receptor agonist. • All adults should be assessed at every healthcare visit for tobacco use, and those who use tobacco should be assisted and strongly advised to quit. • Aspirin should be used infrequently in the routine primary prevention of ASCVD because of lack of net benefit. • Statin therapy is first-line treatment for primary prevention of ASCVD in patients with elevated low-density lipoprotein cholesterol levels (≥190 mg/dL), those with diabetes mellitus, who are 40 to 75 years of age, and those determined to be at sufficient ASCVD risk after a clinician–patient risk discussion. • Nonpharmacological interventions are recommended for all adults with elevated blood pressure or hypertension. For those requiring pharmacological therapy, the target blood pressure should generally be <130/80 mm Hg. <u>Adults with Type 2 Diabetes Mellitus</u> • For all adults with T2DM, a tailored nutrition plan focusing on a heart-healthy dietary pattern is recommended to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors. • Adults with T2DM should perform at least 150 minutes per week of moderate-intensity physical activity or 75 minutes of vigorous-intensity physical activity to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors.

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	• For adults with T2DM, it is reasonable to initiate metformin as first-line therapy along with lifestyle therapies at the time of diagnosis to improve glycemic control and reduce ASCVD risk. • For adults with T2DM and additional ASCVD risk factors who require glucose-lowering therapy despite initial lifestyle modifications and metformin, it may be reasonable to initiate a sodium-glucose cotransporter 2 (SGLT-2) inhibitor or a glucagon-like peptide-1 receptor (GLP-1R) agonist to improve glycemic control and reduce CVD risk. <u>Adults with high blood cholesterol</u> • In adults at intermediate risk (≥7.5% to <20% 10-year ASCVD risk), statin therapy reduces risk of ASCVD, and in the context of a risk discussion, if a decision is made for statin therapy, a moderate-intensity statin should be recommended. • In intermediate risk (≥7.5% to <20% 10-year ASCVD risk) patients, LDL-C levels should be reduced by 30% or more, and for optimal ASCVD risk reduction, especially in patients at high risk (≥20% 10-year ASCVD risk), levels should be reduced by 50% or more. • In adults 40 to 75 years of age with diabetes, regardless of estimated 10-year ASCVD risk, moderate-intensity statin therapy is indicated. • In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL (≥4.9 mmol/L) or higher, maximally tolerated statin therapy is recommended. • In adults with diabetes mellitus who have multiple ASCVD risk factors, it is reasonable to prescribe high-intensity statin therapy with the aim to reduce LDL-C levels by 50% or more. • In intermediate-risk (≥7.5% to <20% 10-year ASCVD risk) adults, risk-enhancing factors favor initiation or intensification of statin therapy. • In intermediate-risk (≥7.5% to <20% 10-year ASCVD risk) adults or selected borderline-risk (5% to <7.5% 10-year ASCVD risk) adults in whom a coronary artery calcium score is measured for the purpose of making a treatment decision, AND o If the coronary artery calcium score is zero, it is reasonable to withhold statin therapy and reassess in five to 10 years, as long as higher-risk conditions are absent (e.g., diabetes, family history of premature CHD, cigarette smoking); o If coronary artery calcium score is one to 99, it is reasonable to initiate statin therapy for patients ≥55 years of age; o If coronary artery calcium score is 100 or higher or in the 75th percentile or higher, it is reasonable to initiate statin therapy. • In patients at borderline risk (5% to <7.5% 10-year ASCVD risk), in risk discussion, the presence of risk-enhancing factors may justify initiation of moderate-intensity statin therapy. <u>Adults with high blood pressure or hypertension</u> • In adults with elevated blood pressure (BP) or hypertension, including those requiring antihypertensive medications nonpharmacological interventions are recommended to reduce BP. These include: o weight loss; o a heart-healthy dietary pattern; o sodium reduction; o dietary potassium supplementation; o increased physical activity with a structured exercise program; and o limited alcohol. • In adults with an estimated 10-year ASCVD risk (ACC/AHA pooled cohort equations to estimate 10-year risk of ASCVD) of 10% or higher and an average

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	systolic BP (SBP) of 130 mm Hg or higher or an average diastolic BP (DBP) of 80 mm Hg or higher, use of BP-lowering medications is recommended for primary prevention of CVD. • In adults with confirmed hypertension and a 10-year ASCVD event risk of 10% or higher, a BP target of less than 130/80 mm Hg is recommended. • In adults with hypertension and chronic kidney disease, treatment to a BP goal of less than 130/80 mm Hg is recommended. • In adults with T2DM and hypertension, antihypertensive drug treatment should be initiated at a BP of 130/80 mm Hg or higher, with a treatment goal of less than 130/80 mm Hg. • In adults with an estimated 10-year ASCVD risk <10% and an SBP of 140 mm Hg or higher or a DBP of 90 mm Hg or higher, initiation and use of BP-lowering medication are recommended. • In adults with confirmed hypertension without additional markers of increased ASCVD risk, a BP target of less than 130/80 mm Hg may be reasonable. <u>Recommendations for treatment of tobacco use</u> • All adults should be assessed at every healthcare visit for tobacco use and their tobacco use status recorded as a vital sign to facilitate tobacco cessation. • To achieve tobacco abstinence, all adults who use tobacco should be firmly advised to quit. • In adults who use tobacco, a combination of behavioral interventions plus pharmacotherapy is recommended to maximize quit rates. • In adults who use tobacco, tobacco abstinence is recommended to reduce ASCVD risk. • To facilitate tobacco cessation, it is reasonable to dedicate trained staff to tobacco treatment in every healthcare system. • All adults and adolescents should avoid secondhand smoke exposure to reduce ASCVD risk. <u>Recommendations for aspirin use</u> • Low-dose aspirin (75 to 100 mg orally daily) might be considered for the primary prevention of ASCVD among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk. • Low-dose aspirin (75 to 100 mg orally daily) should not be administered on a routine basis for the primary prevention of ASCVD among adults >70 years of age. • Low-dose aspirin (75 to 100 mg orally daily) should not be administered for the primary prevention of ASCVD among adults of any age who are at increased risk of bleeding.
American Heart Association/American College of Cardiology/ Heart Failure Society of America: **2022 AHA/ACC /HFSA Guideline for the Management of Heart Failure (2022)[14]**	<u>Treatment of Stage A heart failure (HF)</u> • Hypertension should be controlled in accordance with guideline-directed medication therapy for hypertension to prevent symptomatic HF. (LoE: A) • In patients with type 2 diabetes and either established CVD or at high cardiovascular risk, SGLT-2 inhibitors should be used to prevent hospitalizations for HF. (LoE: A) • In the general population, healthy lifestyle habits such as regular physical activity, maintaining normal weight, healthy dietary patterns, and avoiding smoking are helpful to reduce future risk of HF. (LoE: B) • Patients at risk of developing HF, natriuretic peptide biomarker-based screening followed by team-based care, including a cardiovascular specialist optimizing therapy, can be useful to prevent the development of LV dysfunction (systolic or diastolic) or new-onset HF. (LoE: B) <u>Treatment of Stage B heart failure</u>

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	• In patients with LVEF≤40%, ACE inhibitors should be used to prevent HF and reduce mortality. (LoE: A) • In patients with a recent or remote history of MI or ACS, statins should be used to prevent symptomatic HF and adverse cardiovascular events. (LoE: A) • In patients with a recent MI and LVEF≤40% who are intolerant to ACE inhibitors, ARB should be used to prevent symptomatic HF and reduce mortality. (LoE: B) • In patients with a recent or remote history of MI or ACS and LVEF≤40%, evidence-based beta blockers should be used to reduce mortality. (LoE: B) • In patients who are at least 40 days post-MI with LVEF ≤30% and NYHA class I symptoms while receiving guideline-directed medication therapy and have reasonable expectation of meaningful survival for greater than one year, an implantable cardioverter-defibrillator is recommended for primary prevention of sudden cardiac death to reduce total mortality. (LoE: B) • In patients with LVEF ≤40%, beta blockers should be used to prevent symptomatic HF. (LoE: C) • In patients with LVEF ≤50%, thiazolidinediones should not be used because they increase the risk of HF, including hospitalizations. (LoE: B) • In patients with LVEF ≤50%, nondihydropyridine calcium channel blockers with negative inotropic effects may be harmful. (LoE: C) <u>Treatment for Stage C Heart Failure with Reduced Ejection Fraction (HFrEF)</u> • For patients with stage C HF, avoiding excessive sodium intake is reasonable to reduce congestive symptoms. (LoE: C) • In patients with HF who have fluid retention, diuretics are recommended to relieve congestion, improve symptoms, and prevent worsening HF. (LoE: B) • For patients with HF and congestive symptoms, addition of a thiazide (e.g., metolazone) to treatment with a loop diuretic should be reserved for patients who do not respond to moderate or high dose loop diuretics to minimize electrolyte abnormalities. (LoE: B) • In patients with HFrEF and NYHA class II to III symptoms, the use of an ARNI is recommended to reduce morbidity and mortality. (LoE: A) • In patients with previous or current symptoms of chronic HFrEF, the use of an ACE inhibitor is beneficial to reduce morbidity and mortality when the use of an ARNI is not feasible. (LoE: A) • In patients with previous or current symptoms of chronic HFrEF, who are intolerant to an ACE inhibitor because of cough or angioedema, and when the use of an ARNI is not feasible, the use of an ARB is recommended to reduce morbidity and mortality. (LoE: A) • In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality. (LoE: B) • ARNIs should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor. (LoE: B) • ARNI or ACE inhibitors should not be administered in patients with a history of angioedema. (LoE: C) • In patients with HFrEF, with current or previous symptoms, use of one of the three β-blockers proven to reduce mortality (e.g., bisoprolol, carvedilol, sustained-release metoprolol succinate) is recommended to reduce mortality and hospitalizations. (LoE: A) • In patients with HFrEF and NYHA class II to IV symptoms, a mineralocorticoid receptor antagonist (spironolactone or eplerenone) is recommended to reduce morbidity and mortality, if eGFR is >30 mL/min/1.73 m^2 and serum potassium is <5.0 mEq/L. Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely followed thereafter to minimize risk of hyperkalemia and renal insufficiency. (LoE: A)

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	• In patients taking a mineralocorticoid receptor antagonist whose serum potassium cannot be maintained at <5.5 mEq/L, mineralocorticoid receptor antagonist should be discontinued to avoid life threatening hyperkalemia. (LoE: B) • In patients with symptomatic chronic HFrEF, SGLT-2 an inhibitor is recommended to reduce hospitalization for HF and cardiovascular mortality, irrespective of the presence of type 2 diabetes. (LoE: A) • The combination of hydralazine and isosorbide dinitrate is recommended to improve symptoms and reduce morbidity and mortality for patients self-identified as African Americans with NYHA class III to IV HFrEF receiving optimal therapy. (LoE: A) • In patients with current or previous symptomatic HFrEF who cannot be given first-line agents, such as an ARNI, ACE inhibitor or ARB because of drug intolerance or renal insufficiency, a combination of hydralazine and isosorbide dinitrate might be considered to reduce morbidity and mortality. (LoE: C) • In patients with HF class II to IV symptoms, omega-3 polyunsaturated fatty acid supplementation may be reasonable to use as adjunctive therapy to reduce mortality and cardiovascular hospitalizations. (LoE: B) • In patients with chronic HFrEF without specific indication (e.g., venous thromboembolism, atrial fibrillation, a previous thromboembolic event, or a cardioembolic source, anticoagulation is not recommended. (LoE: B) • Dihydropyridine and non-dihydropyridine calcium channel blockers are not recommended for patients with HFrEF. (LoE: A) • In patients with HFrEF, vitamins, nutritional supplements, and hormonal therapy are not recommended other than to correct specific deficiencies. (LoE: B) • In patients with HFrEF, class IC antiarrhythmic medication and dronedarone may increase risk of mortality. (LoE: A) • In patients with HFrEF, thiazolidinediones increase the risk of worsening HF symptoms and hospitalizations. (LoE: A) • In patients with type 2 diabetes and high cardiovascular risk, the DPP-4 inhibitors, saxagliptin and alogliptin, increase the risk of HF hospitalization and should be avoided in patients with HF. (LoE: B) • In patients with HFrEF, nonsteroidal anti-inflammatory drugs worsen HF symptoms and should be avoided or withdrawn whenever possible. (LoE: B) • For patients with symptomatic (NYHA class II to III) stable chronic HFrEF (LVEF ≤35%) who are receiving guideline-directed medical therapy, including a maximally tolerated dose of a beta blocker, and who are in sinus rhythm with a heart rate of ≥70 beats per minute at rest, ivabradine can be beneficial to reduce HF hospitalizations and cardiovascular death. (LoE: B) • In patients with symptomatic HFrEF despite guideline-directed medical therapy or who are unable to tolerate guideline-directed medical therapy, digoxin might be considered to decrease hospitalizations for HF. (LoE: B) • In select high-risk patients with HFrEF and recent worsening of HF already on guideline-directed medical therapy, an oral soluble guanylate cyclase stimulator (vericiguat) may be considered to reduce HF hospitalization and cardiovascular death. (LoE: B) <u>Pharmacological treatment for Stage C HF with mildly reduced EF and improved EF</u> • In patients with HF with mildly reduced EF, SGLT-2 inhibitors can be beneficial in decreasing HF hospitalizations and cardiovascular mortality. (LoE: B) • Among patients with current or previous symptomatic HF with mildly reduced EF (LVEF, 41 to 49%), use of evidence-based beta blockers for HFrEF, ARNI, ACE inhibitor or ARB, and mineralocorticoid receptor antagonists may be considered to reduce the risk of HF hospitalization and cardiovascular mortality, particularly among patients with LVEF on the lower end of this spectrum. (LoE: B) • In patients with HF with improved EF after treatment, guideline-directed medical

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	therapy should be continued to prevent relapse of HF and LV dysfunction, even in patients who may become asymptomatic. (LoE: B) <u>Pharmacological treatment for Stage C HF with preserved EF (HFpEF)</u> • Patients with hypertension and HFpEF should have medication titrated to attain blood pressure targets in accordance with published clinical practice guidelines to prevent morbidity. (LoE: C) • SGLT-2 inhibitors can be beneficial in decreasing HF hospitalizations and cardiovascular mortality. (LoE: B) • In patients with HFpEF, the use of a mineralocorticoid receptor antagonist, ARB, or ARNI may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum. (LoE: B) • Routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or quality of life in patients with HFpEF is ineffective. (LoE: B) <u>Treatment of Stage D (advanced/refractory) HF</u> • For patients with advanced HF and hyponatremia, the benefit of fluid restriction to reduce congestive symptoms is uncertain. (LoE: C) • Continuous intravenous inotropic support is reasonable as "bridge therapy" in patients with HF (Stage D) refractory to guideline-directed medical therapy and device therapy who are eligible for and awaiting mechanical circulatory support or cardiac transplantation. (LoE: B) • In select patients with HF Stage D, despite optimal guideline-directed medical therapy and device therapy who are ineligible for either mechanical circulatory support or cardiac transplantation, continuous intravenous inotropic support may be considered as palliative therapy for symptom control and improvement in functional status. (LoE: B) • Long-term use of either continuous or intermittent, intravenous inotropic agents, for reasons other than palliative care or as a bridge to advanced therapies, is potentially harmful. (LoE: B)
European Society of Cardiology: **Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (2021)**[15]	<u>Pharmacological treatments indicated in patients with (NYHA Class II-IV) heart failure with reduced ejection fraction</u> • An ACE inhibitor is recommended, in addition to a β-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death. • A mineralocorticoid receptor antagonist (MRA) is recommended for patients with HFrEF, who remain symptomatic despite treatment with an ACE inhibitor and a β-blocker, to reduce the risk of HF hospitalization and death. • Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death. Dapagliflozin or empagliflozin are recommended, in addition to optimal medical therapy with an ACE-I/ARNI, a β-blocker and an MRA, for patients with HFrEF regardless of diabetes status. • Sacubitril-valsartan is recommended as a replacement for an ACE inhibitor to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE inhibitor, a β-blocker, and a mineralocorticoid receptor antagonist. • Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion. • Ivabradine should be considered to reduce the risk of HF hospitalization or cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm despite treatment with an evidence-based dose of β-blocker (or maximum tolerated dose below that), ACE inhibitor (or ARB), and a mineralocorticoid receptor antagonist (or ARB). • Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm who are unable to tolerate or have

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	contraindications for a β-blocker. Patients should also receive an ACE inhibitor (or ARB) and a mineralocorticoid receptor antagonist (or ARB). • An ARB is recommended to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients unable to tolerate an ACE inhibitor (patients should also receive a β-blocker and mineralocorticoid receptor antagonist). • An ARB may be considered to reduce the risk of HF hospitalization and death in patients who are symptomatic despite treatment with a β-blocker who are unable to tolerate a mineralocorticoid receptor antagonist. • Vericiguat may be considered in patients in NYHA class II-IV who have had worsening HF despite treatment with an ACE-I (or ARNI), a β-blocker and an MRA to reduce the risk of CV mortality or HF hospitalization. • Hydralazine and isosorbide dinitrate should be considered in self-identified black patients with LVEF ≤35% or with an LVEF <45% combined with a dilated LV in NYHA Class III–IV despite treatment with an ACE-I a β-blocker and a mineralocorticoid receptor antagonist to reduce the risk of HF hospitalization and death. • Hydralazine and isosorbide dinitrate may be considered in symptomatic patients with HFrEF who can tolerate neither an ACE inhibitor nor an ARB (or they are contraindicated) to reduce the risk of death. • Digoxin is a treatment with less-certain benefits and may be considered in symptomatic patients in sinus rhythm despite treatment with an ACE inhibitor (or ARB), a β-blocker and a mineralocorticoid receptor antagonist, to reduce the risk of hospitalization (both all-cause and HF-hospitalizations). <u>Recommendations for treatment of patients with (NYHA class II-IV) heart failure with mildly reduced ejection fraction (HFmrEF)</u> • Diuretics are recommended in patients with congestion and HFmrEF in order to alleviate symptoms and signs. • An ACE inhibitor may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • An ARB may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • A β-blocker may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • An MRA may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • Sacubitril/valsartan may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. <u>Recommendations for treatment of patients with heart failure with preserved ejection fraction (HFpEF)</u> • It is recommended to screen patients with HFpEF for both cardiovascular and noncardiovascular comorbidities, which, if present, should be treated provided safe and effective interventions exist to improve symptoms, well-being and/or prognosis. • Diuretics are recommended in congested patients with HFpEF in order to alleviate symptoms and signs. <u>Recommendations for the primary prevention of heart failure in patients with risk factors for its development</u> • Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life. • Treatment with statins is recommended in patients at high risk of CV disease or with CV disease in order to prevent or delay the onset of HF, and to prevent HF

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	hospitalizations. • SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with diabetes at high risk of CV disease or with CV disease in order to prevent HF hospitalizations. • Counselling against sedentary habit, obesity, cigarette smoking, and alcohol abuse is recommended to prevent or delay the onset of HF. <u>Recommendations for the initial management of patients with acute heart failure – pharmacotherapy</u> • Intravenous loop diuretics are recommended for all patients with acute HF admitted with signs/symptoms of fluid overload to improve symptoms. It is recommended to regularly monitor symptoms, urine output, renal function and electrolytes during use of intravenous diuretics. • Combination of a loop diuretic with thiazide type diuretic should be considered in patients with resistant oedema who do not respond to an increase in loop diuretic doses. • In patients with acute HF and SBP >110 mmHg, intravenous vasodilators may be considered as initial therapy to improve symptoms and reduce congestion. • Inotropic agents may be considered in patients with SBP <90 mmHg and evidence of hypoperfusion who do not respond to standard treatment, including fluid challenge, to improve peripheral perfusion and maintain end-organ function. • Inotropic agents are not recommended routinely, due to safety concerns, unless the patient has symptomatic hypotension and evidence of hypoperfusion. • A vasopressor, preferably norepinephrine, may be considered in patients with cardiogenic shock to increase blood pressure and vital organ perfusion. • Thromboembolism prophylaxis (e.g., with LMWH) is recommended in patients not already anticoagulated and with no contraindication to anticoagulation, to reduce the risk of deep venous thrombosis and pulmonary embolism. • Routine use of opiates is not recommended, unless in selected patients with severe/intractable pain or anxiety.
American Heart Association/ American College of Cardiology/ Heart Rhythm Society: **2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation (2023)[16]**	<u>Top 10 Take-Home Messages</u> • Stages of atrial fibrillation (AF): The previous classification of AF, which was based only on arrhythmia duration, although useful, tended to emphasize therapeutic interventions. The new proposed classification, using stages, recognizes AF as a disease continuum that requires a variety of strategies at the different stages, from prevention, lifestyle and risk factor modification, screening, and therapy. • AF risk factor modification and prevention: This guideline recognizes lifestyle and risk factor modification as a pillar of AF management to prevent onset, progression, and adverse outcomes. The guideline emphasizes risk factor management throughout the disease continuum and offers more prescriptive recommendations, accordingly, including management of obesity, weight loss, physical activity, smoking cessation, alcohol moderation, hypertension, and other comorbidities. • Flexibility in using clinical risk scores and expanding beyond CHA2DS2-VASc for prediction of stroke and systemic embolism: Recommendations for anticoagulation are now made based on yearly thromboembolic event risk using a validated clinical risk score, such as CHA2DS2-VASc. However, patients at an intermediate annual risk score who remain uncertain about the benefit of anticoagulation can benefit from consideration of other risk variables to help inform the decision, or the use of other clinical risk scores to improve prediction, facilitate shared decision making, and incorporate into the electronic medical record. • Consideration of stroke risk modifiers: Patients with AF at intermediate to low (<2%) annual risk of ischemic stroke can benefit from consideration of factors that

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	might modify their risk of stroke, such as the characteristics of their AF (e.g., burden), nonmodifiable risk factors (sex), and other dynamic or modifiable factors (blood pressure control) that may inform shared decision-making discussions. • Early rhythm control: With the emergence of new and consistent evidence, this guideline emphasizes the importance of early and continued management of patients with AF that should focus on maintaining sinus rhythm and minimizing AF burden. • Catheter ablation of AF receives a Class 1 indication as first-line therapy in selected patients: Recent randomized studies have demonstrated the superiority of catheter ablation over drug therapy for rhythm control in appropriately selected patients. In view of the most recent evidence, we upgraded the Class of Recommendation. • Catheter ablation of AF in appropriate patients with heart failure with reduced ejection fraction receives a Class 1 indication: Recent randomized studies have demonstrated the superiority of catheter ablation over drug therapy for rhythm control in patients with heart failure and reduced ejection failure. In view of the data, we upgraded the Class of Recommendation for this population of patients. • Recommendations have been updated for device-detected AF: In view of recent studies, more prescriptive recommendations are provided for patients with device-detected AF that consider the interaction between episode duration and the patient's underlying risk for thromboembolism. This includes considerations for patients with AF detected via implantable devices and wearables. • Left atrial appendage occlusion devices receive higher level Class of Recommendation: In view of additional data on safety and efficacy of left atrial appendage occlusion devices, the Class of Recommendation has been upgraded to 2a compared with the 2019 AF Focused Update for use of these devices in patients with long-term contraindications to anticoagulation. • Recommendations are made for patients with AF identified during medical illness or surgery (precipitants): Emphasis is made on the risk of recurrent AF after AF is discovered during noncardiac illness or other precipitants, such as surgery. <u>Prevention of Thromboembolism</u> • Recommendations for Antithrombotic Therapy ○ For patients with atrial fibrillation (AF) and an estimated annual thromboembolic risk of ≥2% per year (e.g., CHA2DS2-VASc score of ≥2 in men and ≥3 in women), anticoagulation is recommended to prevent stroke and systemic thromboembolism. ○ In patients with AF who do not have a history of moderate to severe rheumatic mitral stenosis or a mechanical heart valve, and who are candidates for anticoagulation, direct oral anticoagulants (DOACs) are recommended over warfarin to reduce the risk of mortality, stroke, systemic embolism, and intracranial hemorrhage (ICH). ○ For patients with AF and an estimated annual thromboembolic risk of ≥1% but <2% per year (equivalent to CHA2DS2-VASc score of 1 in men and 2 in women), anticoagulation is reasonable to prevent stroke and systemic thromboembolism. ○ In patients with AF who are candidates for anticoagulation and without an indication for antiplatelet therapy, aspirin either alone or in combination with clopidogrel as an alternative to anticoagulation is not recommended to reduce stroke risk. ○ In patients with AF without risk factors for stroke, aspirin monotherapy for prevention of thromboembolic events is of no benefit. • Considerations in Managing Anticoagulants ○ For patients with AF receiving DOACs, optimal management of drug interactions is recommended for those receiving concomitant therapy with interacting drugs, especially CYP3A4 and/or p-glycoprotein inhibitors or

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	inducers. ○ For patients with AF receiving warfarin, (excludes patients with mechanical valves) a target INR between 2 and 3 is recommended, as well as optimal management of drug-drug interactions, consistency in vitamin K dietary intake, and routine INR monitoring to improve time in therapeutic range and to minimize risks of preventable thromboembolism or major bleeding. ○ and to minimize risks of preventable thromboembolism or major bleeding. ○ For patients with AF, nonevidence-based doses of DOACs should be avoided to minimize risks of preventable thromboembolism or major bleeding and to improve survival. • Recommendations for AF Complicating acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) ○ In patients with AF and an increased risk for stroke who undergo PCI, DOACs are preferred over vitamin K antagonists (VKAs) in combination with antiplatelet therapy (APT) to reduce the risk of clinically relevant bleeding. ○ In most patients with AF who take oral anticoagulation and undergo PCI, early discontinuation of aspirin (one to four weeks) and continuation of dual antithrombotic therapy with oral anticoagulant (OAC) and a P2Y12 inhibitor is preferred over triple therapy (OAC, P2Y12 inhibitor, and aspirin) to reduce the risk of clinically relevant bleeding. ○ rin) to reduce the risk of clinically relevant bleeding. • Recommendation for Chronic Coronary Disease (CCD) ○ In patients with AF and CCD (beyond one year after revascularization or coronary artery disease (CAD) not requiring coronary revascularization) without history of stent thrombosis, oral anticoagulation monotherapy is recommended over the combination therapy of OAC and single APT (aspirin or P2Y12 inhibitor) to decrease the risk of major bleeding. • Recommendation for Peripheral Artery Disease (PAD) ○ In patients with AF and concomitant stable PAD, monotherapy oral anticoagulation is reasonable over dual therapy (anticoagulation plus aspirin or P2Y12 inhibitors) to reduce the risk of bleeding. • Recommendations for Chronic Kidney Disease (CKD)/Kidney Failure ○ For patients with AF at elevated risk for stroke and CKD stage 3, treatment with warfarin or, preferably, evidence-based doses of direct thrombin or factor Xa inhibitors is recommended to reduce the risk of stroke. ○ For patients with AF at elevated risk for stroke and CKD stage 4, treatment with warfarin or labeled doses of DOACs is reasonable to reduce the risk of stroke. ○ For patients with AF at elevated risk for stroke and who have end-stage CKD (CrCl <15 mL/min) or are on dialysis, it might be reasonable to prescribe warfarin (INR 2.0 to 3.0) or an evidence-based dose of apixaban for oral anticoagulation to reduce the risk of stroke. • Recommendations for AF in valvular heart disease (VHD) ○ In patients with rheumatic mitral stenosis or mitral stenosis of moderate or greater severity and history of AF, long-term anticoagulation with warfarin is recommended over DOACs, independent of the CHA2DS2-VASc score to prevent cardiovascular events, including stroke or death. ○ In patients with AF and valve disease other than moderate or greater mitral stenosis or a mechanical heart valve, DOACs are recommended over VKAs. <u>Rate control</u> • Broad Considerations for Rate Control ○ In patients with AF, shared decision-making with the patient is recommended to discuss rhythm- versus rate-control strategies (taking into consideration clinical presentation, comorbidity burden, medication profile, and patient

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	preferences), discuss therapeutic options, and for assessing long-term benefits. ○ In patients with AF without HF who are candidates for select rate-control strategies, heart rate target should be guided by underlying patient symptoms, in general aiming at a resting heart rate of <100 to 110 bpm. ○ to 110 bpm. • Recommendations for Acute Rate Control ○ In patients with AF with rapid ventricular response who are hemodynamically stable, beta blockers or nondihydropyridine calcium channel blockers (verapamil, diltiazem; provided that EF >40%) are recommended for acute rate control. ○ In patients with AF with rapid ventricular response in whom beta blockers and nondihydropyridine calcium channel blockers are ineffective or contraindicated, digoxin can be considered for acute rate control, either alone or in combination with the aforementioned agents. ○ In patients with AF with rapid ventricular response, the addition of intravenous magnesium to standard rate-control measures is reasonable to achieve and maintain rate control. ○ In patients with AF with rapid ventricular response who are critically ill and/or in decompensated HF in whom beta blockers and nondihydropyridine calcium channel blockers are ineffective or contraindicated, intravenous amiodarone may be considered for acute rate control. Consider the risk of cardioversion and stroke when using amiodarone as a rate-control agent. ○ arone as a rate-control agent. ○ In patients with AF with rapid ventricular response and known moderate or severe LV systolic dysfunction with or without decompensated HF, intravenous nondihydropyridine calcium channel blockers should not be administered. • Recommendations for Long-Term Rate Control ○ In patients with AF, beta blockers or nondihydropyridine calcium channel blockers (diltiazem, verapamil) are recommended for long-term rate control with the choice of agent according to underlying substrate and comorbid conditions. ○ For patients with AF in whom measuring serum digoxin levels is indicated, it is reasonable to target levels <1.2 ng/mL. ○ In patients with AF and HF symptoms, digoxin is reasonable for long-term rate control in combination with other rate-controlling agents, or as monotherapy if other agents are not preferred, not tolerated, or contraindicated. ○ In patients with AF and LVEF <40%, nondihydropyridine calcium channel–blocking drugs should not be administered given their potential to exacerbate HF. ○ In patients with permanent AF who have risk factors for cardiovascular events, dronedarone should not be used for long-term rate control. <u>Rhythm Control</u> • Recommendations for Pharmacological Cardioversion ○ For patients with AF, pharmacological cardioversion is reasonable as an alternative to electrical cardioversion for those who are hemodynamically stable or in situations when electrical cardioversion is preferred but cannot be performed. ○ For patients with AF, ibutilide is reasonable for pharmacological cardioversion for patients without depressed LV function (LVEF <40%). ○ For patients with AF, intravenous amiodarone is reasonable for pharmacological cardioversion, although time to conversion is generally longer than with other agents (8-12 hours).

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	○ For patients with recurrent AF occurring outside the setting of a hospital, the "pill-in-the-pocket" (PITP) approach with a single oral dose of flecainide or propafenone, with a concomitant atrioventricular nodal blocking agent, is reasonable for pharmacological cardioversion if previously tested in a monitored setting. ○ For patients with AF, use of intravenous procainamide may be considered for pharmacological cardioversion when other intravenous agents are contraindicated or not preferred. • Recommendations for Specific Drug Therapy for Long-Term Maintenance of Sinus Rhythm ○ For patients with AF and HFrEF (≤40%), therapy with dofetilide or amiodarone is reasonable for long-term maintenance of sinus rhythm. ○ For patients with AF and no previous MI, or known or suspected significant structural heart disease, or ventricular scar or fibrosis, use of flecainide or propafenone is reasonable for long-term maintenance of sinus rhythm. ○ For patients with AF without recent decompensated HF or severe LV dysfunction, use of dronedarone is reasonable for long-term maintenance of sinus rhythm. ○ For patients with AF without significant baseline QT interval prolongation or uncorrected hypokalemia or hypomagnesemia, use of dofetilide is reasonable for long-term maintenance of sinus rhythm, with proper dose selection based on kidney function and close monitoring of the QT interval, serum potassium and magnesium concentrations, and kidney function. ○ For patients with AF and normal LV function, use of low-dose amiodarone (100 to 200 mg/d) is reasonable for long-term maintenance of sinus rhythm but, in view of its adverse effect profile, should be reserved for patients in whom other rhythm control strategies are ineffective, not preferred, or contraindicated. ○ of its adverse effect profile, should be reserved for patients in whom other rhythm control strategies are ineffective, not preferred, or contraindicated. ○ For patients with AF without significant baseline QT interval prolongation, hypokalemia, hypomagnesemia, or bradycardia, use of sotalol may be considered for long-term maintenance of sinus rhythm, with proper dose selection based on kidney function and close monitoring of the QT interval, heart rate, serum potassium and magnesium concentrations, and kidney function. ○ In patients with previous MI and/or significant structural heart disease, including HFrEF (LVEF ≤40%), flecainide and propafenone should not be administered due to the risk of worsening HF, potential proarrhythmia, and increased mortality. ○ For patients with AF, dronedarone should not be administered for maintenance of sinus rhythm to those with NYHA class III and IV HF or patients who have had an episode of decompensated HF in the past 4 weeks, due to the risk of increased early mortality associated with worsening HF. <u>Management of Patients With HF</u> • Recommendations for Management of AF in Patients With HF ○ In patients who present with a new diagnosis of HFrEF and AF, arrhythmia-induced cardiomyopathy should be suspected, and an early and aggressive approach to AF rhythm control is recommended. ○ In appropriate patients with AF and HFrEF who are on guideline-directed management and therapy, and with reasonable expectation of procedural benefit, catheter ablation is beneficial to improve symptoms, quality of life, ventricular function, and cardiovascular outcomes. ○ In appropriate patients with symptomatic AF and HFpEF with reasonable expectation of benefit, catheter ablation can be useful to improve symptoms

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	and improve quality of life. ○ In patients with AF and HF, digoxin is reasonable for rate control, in combination with other rate-controlling agents or as monotherapy if other agents are not tolerated. ○ In patients with AF and HF with rapid ventricular rates in whom beta blockers or calcium channel blockers are contraindicated or ineffective, intravenous amiodarone is reasonable for acute rate control. ○ In patients with AF, HFrEF (LVEF <50%), and refractory rapid ventricular response who are not candidates for or in whom rhythm control has failed, atrioventricular nodal ablation (AVNA) and biventricular pacing therapy can be useful to improve symptoms, quality of life, and EF. ○ In patients with AF, HF, and implanted biventricular pacing therapy in whom an effective pacing percentage cannot be achieved with pharmacological therapy, AVNA can be beneficial to improve functional class, reduce the risk of ICD shock, and improve survival. ○ ock, and improve survival. ○ In patients with AF-induced cardiomyopathy who have recovered LV function, long-term surveillance can be beneficial to detect recurrent AF in view of the high risk of recurrence of arrhythmia-induced cardiomyopathy. ○ In patients with suspected AF-induced cardiomyopathy or refractory HF symptoms undergoing pharmacological rate-control therapy for AF, a stricter rate-control strategy (target heart rate <80 bpm at rest and <110 bpm during moderate exercise) may be reasonable. ○ In patients with AF and HFrEF who undergo AVNA, conduction system pacing of the His bundle or left bundle branch area may be reasonable as an alternative to biventricular pacing to improve symptoms, quality of life, and LV function. ○ In patients with AF and known LVEF <40%, nondihydropyridine calcium channel–blocking drugs should not be administered because of their potential to exacerbate HF. ○ For patients with AF, dronedarone should not be administered for maintenance of sinus rhythm to those with NYHA class III and IV HF or patients who have had an episode of decompensated HF in the past four weeks, due to the risk of increased early mortality associated with worsening HF.
National Institute for Health and Care Excellence: **Atrial Fibrillation: Diagnosis and Management (2021)**[17]	<u>Rate control</u> • Offer rate control as the first-line treatment strategy for atrial fibrillation except in people: ○ whose atrial fibrillation has a reversible cause ○ who have heart failure thought to be primarily caused by atrial fibrillation ○ with new-onset atrial fibrillation ○ with atrial flutter whose condition is considered suitable for an ablation strategy to restore sinus rhythm ○ for whom a rhythm-control strategy would be more suitable based on clinical judgement. • Offer either a standard β-blocker (that is, a β-blocker other than sotalol) or a rate-limiting calcium channel blocker (CCB) (diltiazem or verapamil) as initial monotherapy to people with atrial fibrillation (AF) unless the person has the features described above. Base the choice of drug on the person's symptoms, heart rate, comorbidities and preferences. • Consider digoxin monotherapy for initial rate control for people with non-paroxysmal atrial fibrillation if the person does no or very little physical exercise or if other rate-limiting drug options are ruled out because of comorbidities or the person's preferences. • If monotherapy does not control symptoms, and if continuing symptoms are thought to be due to poor ventricular rate control, consider combination therapy

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	with any two of the following: a β-blocker, diltiazem, and digoxin. • Do not offer amiodarone for long-term rate control. <u>Rhythm control</u> • Consider pharmacological and/or electrical rhythm control for people with AF whose symptoms continue after heart rate has been controlled or for whom a rate-control strategy has not been successful. <u>Drug treatment for long-term rhythm control</u> • Assess the need for drug treatment for long-term rhythm control, taking into account the person's preferences, associated comorbidities, risks of treatment, and likelihood of recurrence of AF. • Do not offer class 1c antiarrhythmic drugs such as flecainide or propafenone to people with known ischaemic or structural heart disease. • If drug treatment for long-term rhythm control is needed, consider a standard β-blocker as first-line treatment unless there are contraindications. • If β-blockers are contraindicated or unsuccessful, assess the suitability of alternative drugs for rhythm control, taking comorbidities into account. • Dronedarone is recommended as an option for the maintenance of sinus rhythm after successful cardioversion in people with paroxysmal or persistent atrial fibrillation: o Whose AF is not controlled by first-line therapy (usually including β-blockers), that is, as a second-line treatment option and after alternative options have been considered AND o Who have at least one of the following cardiovascular risk factors: ▪ Hypertension requiring drugs of at least two different classes. ▪ Diabetes mellitus. ▪ Previous TIA, stroke, or systemic embolism. ▪ Left atrial diameter of 50 mm or greater, OR ▪ Age ≥70 years, AND o Who do not have left ventricular systolic dysfunction, AND o Who do not have a history of, or current, heart failure. • People who do not meet the criteria above who are currently receiving dronedarone should have the option to continue treatment until they and their clinicians consider it appropriate to stop. • Consider amiodarone for people with left ventricular impairment or heart failure. • Do not offer class 1c antiarrhythmic drugs such as flecainide or propafenone to people with known ischemic or structural heart disease. • Where people have infrequent paroxysms and few symptoms, or where symptoms are induced by known precipitants (such as alcohol, caffeine), a 'no drug treatment' strategy or a 'pill-in-the-pocket' strategy should be considered and discussed with the person. <u>Preventing postoperative atrial fibrillation</u> • In people having cardiothoracic surgery: o reduce the risk of postoperative atrial fibrillation by offering one of the following: amiodarone; a standard beta-blocker (that is, a beta-blocker other than sotalol); a rate-limiting calcium-channel blocker (diltiazem or verapamil). o do not offer digoxin. • In people having cardiothoracic surgery who are already on beta-blocker therapy, continue this treatment unless contraindications develop (such as postoperative bradycardia or hypotension). • Do not start statins in people having cardiothoracic surgery solely to prevent postoperative atrial fibrillation.

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	• In people having cardiothoracic surgery who are already on statins, continue this treatment. For further advice on statins for the prevention of cardiovascular disease, see NICE's guideline on cardiovascular disease: risk assessment and reduction.
American Association for Thoracic Surgery: **2014 AATS Guidelines for the Prevention and Management of Peri-Operative Atrial Fibrillation and Flutter (POAF) for Thoracic Surgical Procedures (2014)[18]**	<u>Recommended prevention strategies for all postoperative atrial fibrillation (POAF) patients</u> • Patients taking β-blockers prior to thoracic surgery should continue them in the postoperative period to avoid β-blockade withdrawal. • Intravenous magnesium supplementation may be considered to prevent postoperative AF when serum magnesium level is low or it is suspected that total body magnesium is depleted. • Digoxin should not be used for prophylaxis against AF. <u>Recommended prevention strategies for intermediate to high-risk POAF patients</u> • It is reasonable to administer diltiazem to those patients with preserved cardiac function who are not taking β-blockers preoperatively in order to prevent POAF. • It is reasonable to consider the postoperative administration of amiodarone to reduce the incidence of POAF for intermediate and high risk patients undergoing pulmonary resection. • Postoperative administration of intravenous amiodarone may be considered to prevent POAF in patients undergoing esophagectomy. • Atorvastatin may be considered to prevent POAF for statin naïve patients scheduled for intermediate and high risk thoracic surgical procedures. <u>Rate control recommendations for patients with new onset POAF</u> • Intravenous administration of β-blockers (e.g., esmolol or metoprolol) or nondihydropyridine calcium channel blockers (diltiazem or verapamil) is recommended to achieve rate control (heart rate ≤110 bpm) for patients who develop POAF with rapid ventricular response. • Caution should be used with patients with hypotension, left ventricular (LV) dysfunction, or heart failure. • Combination use of atrioventricular (AV) nodal blocking agents, such as β-blockers (e.g., esmolol or metoprolol), nondihydropyridine calcium channel antagonists (e.g., diltiazem or verapamil), or digoxin, can be useful to control heart rates when a single agent fails to control rates of POAF. The choice should be individualized and doses modified to avoid bradycardia. • For patients with hypotension, heart failure or LV dysfunction, or when other measures are unsuccessful or contraindicated, intravenous amiodarone can be useful for control of heart rate. Amiodarone could result in conversion to sinus rhythm, and if it is initiated after 48 hours of AF, both a transesophageal echocardiography (TEE) when possible, to rule out left atrial/LA appendage (LA/LAA) thrombus, and full anticoagulation should be considered. • For patients with heart failure, LV dysfunction or hypotension, intravenous digoxin may be considered for rate control of POAF. • For patients with ventricular preexcitation (i.e., Wolff-Parkinson-White syndrome) and POAF, use of AV nodal blocking agents, such as β-blockers (e.g., esmolol or metoprolol), intravenous amiodarone, nondihydropyridine calcium channel antagonists (e.g., diltiazem or verapamil), or digoxin, should be avoided. <u>Recommendations for the use of antiarrhythmic drugs for pharmacologic cardioversion of POAF</u> • Restoration of sinus rhythm with pharmacologic cardioversion is reasonable in patients with symptomatic, hemodynamically stable POAF. Intravenous amiodarone can be useful for pharmacologic cardioversion of POAF. • It is reasonable to administer antiarrhythmic medications in an attempt to maintain

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	sinus rhythm for patients with recurrent or refractory POAF. • Amiodarone, sotalol, flecainide, propafenone, or dofetilide can be useful to maintain sinus rhythm in patients with POAF, depending on underlying heart disease, renal status and other comorbidities. • Flecainide or propafenone may be considered for pharmacologic cardioversion of POAF and maintenance of sinus rhythm if the patient has had no prior history of myocardial infarction, coronary artery disease, impaired LV function, significant LV hypertrophy, or valvular heart disease that is considered moderate or greater. These agents may need to be combined with an AV nodal blocking agent. • Intravenous ibutilide or procainamide may be considered for pharmacologic conversion of POAF for patients with structural heart disease and new onset POAF, but no hypotension or manifestations of congestive heart failure. Serum electrolytes and QTc interval must be within a normal range and patients must be closely monitored during and for at least six hours after the infusion if either ibutilide or procainamide. • Intravenous ibutilide or procainamide may be considered for patients with POAF and an accessory pathway. • Flecainide and propafenone should not be used to treat POAF in patients with a history of a prior myocardial infarction, coronary artery disease, and/or severe structural heart disease, including severe left ventricular hypertrophy, or significantly reduced left ventricular ejection fraction. • Dronedarone should not be used for treatment of POAF in patients with heart failure. <u>Recommendations for prevention of thromboembolism for patients with stable atrial fibrillation/flutter undergoing direct current cardioversion</u> • For stable patients with POAF of 48-hours duration or longer, anticoagulation (with warfarin for INR 2.0 to 3.0, a novel oral anti-coagulant [NOAC] or LMWH) is recommended for at least three weeks prior to and four weeks after cardioversion, regardless of the method (electrical or pharmacological) used to restore sinus rhythm. • During the first 48 hours after the onset of POAF, the need for anticoagulation before and after direct current (DC) cardioversion may be based on the patient's risk of thromboembolism (CHA_2DS_2-VASc score) balanced by the risk of postoperative bleeding. • For POAF lasting longer than 48 hours, as an alternative to three weeks of therapeutic anticoagulation prior to cardioversion of POAF, it is reasonable to perform TEE in search of thrombus in the LA or LA appendage, preferably with full anticoagulation at the time of TEE in anticipation of DC cardioversion after the TEE. • For POAF lasting longer than 48 hours in patients who are not candidates for TEE (e.g., post-esophageal surgery), an initial rate control strategy combined with therapeutic anticoagulation using warfarin (aiming for INR 2.0 to 3.0), a direct thrombin inhibitor (e.g. dabigatran), factor Xa inhibitor (e.g. rivaroxaban, apixaban), or LMWH is recommended for at least three weeks prior to and four weeks after cardioversion. • Anticoagulation recommendations for cardioversion of atrial flutter are similar to those for atrial fibrillation. • For patients with an identified thrombus, cardioversion should not be performed until a longer period of anticoagulation is achieved (usually at least three weeks) and in accordance with established AF guidelines. <u>Management of anticoagulation for new onset POAF</u> • For the prevention of strokes for patients who develop POAF lasting longer than 48 hours, it is recommended to administer antithrombotic medications similarly to

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	non-surgical patients. Anticoagulation within the first 48-hours of POAF should be considered based on the CHA_2DS_2-VASc risk score of the patient for stroke weighed against the risk of postoperative bleeding. • New oral anticoagulants (dabigatran, rivaroxaban, apixaban) are reasonable as an alternative to warfarin for patients who do not have a prosthetic heart valve, hemodynamically significant valve disease, and/or severe renal impairment or risk of GI bleeding. • It is reasonable to continue anticoagulation therapy for four weeks after the return of sinus rhythm because of the possibility of slowly resolving impairment of atrial contraction with an associated ongoing risk for thrombus formation and for delayed embolic events. • New oral anticoagulants should be avoided for patients at risk for serious bleeding (including GI bleeding) as they cannot be readily reversed. However, their use may be recommended in situations where achievement of a therapeutic INR with warfarin has proved to be difficult.
American College of Cardiology/ American Heart Association/ European Society of Cardiology Committee for Practice Guidelines: **Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death (2017)**[19]	<u>Recommendation for Pharmacological Prevention of Sudden Cardiac Death (SCD)</u> <u>Class I recommendation</u> • In patients with heart failure with reduced ejection fraction (HFrEF, ≤40%), treatment with a β-blocker, a mineralocorticoid receptor antagonist and either an angiotensin-converting enzyme (ACE) inhibitor, an angiotensin-receptor blocker (ARB), or an angiotensin receptor-neprilysin inhibitor (ARNI) is recommended to reduce SCD and all-cause mortality. <u>Recommendations for Autonomic Modulation</u> <u>Class IIa recommendation</u> • In patients with symptomatic, non-life threatening ventricular arrhythmia (VA), treatment with a β-blocker is reasonable. <u>Class IIb recommendation</u> • In patients with ventricular tachycardia (VT)/ ventricular fibrillation (VF) storm in whom a a β-blocker, other antiarrhythmic medications, and catheter ablation are ineffective, not tolerated, or not possible, cardiac sympathetic denervation may be reasonable. <u>Recommendation for Management of Cardiac Arrest</u> <u>Class I recommendation</u> • Cardiopulmonary resuscitation (CPR) should be performed in patients in cardiac arrest according to published basic and advanced cardiovascular life support algorithms. • In patients with hemodynamically unstable VA that persist or recur after a maximal energy shock, intravenous amiodarone should be administered to attempt to achieve a stable rhythm after further defibrillation. • Patients presenting with VA with hemodynamic instability should undergo direct current cardioversion. • In patients with polymorphic VT or VF with ST-elevation myocardial infarction (MI), angiography with emergency revascularization is recommended. • Patients with a wide-QRS tachycardia should be presumed to have VT if the diagnosis is unclear. <u>Class IIa recommendation</u> • In patients with hemodynamically stable VT, administration of intravenous procainamide can be useful to attempt to terminate VT. • In patients with a witnessed cardiac arrest due to VF or polymorphic VT that is unresponsive to CPR, defibrillation, and vasopressor therapy, intravenous lidocaine can be beneficial. • In patients with polymorphic VT due to myocardial ischemia, intravenous β-blockers can be useful.

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	• In patients with a recent MI who have VT/VF that repeatedly recurs despite direct current cardioversion and antiarrhythmic medications (VT/VF storm), an intravenous β-blocker can be useful. Class IIb recommendation • In patients in cardiac arrest, administration of epinephrine (1 mg every 3 to 5 minutes) during CPR may be reasonable. • In patients with hemodynamically stable VT, administration of intravenous amiodarone or sotalol may be considered to attempt to terminate VT. Class III: No benefit recommendation • In patients with cardiac arrest, administration of high-dose epinephrine (>1 mg boluses) compared with standard doses is not beneficial. • In patients with refractory VF not related to torsades de pointes, administration of intravenous magnesium is not beneficial. Class III: harm recommendation • In patients with suspected acute myocardial infarction (AMI), prophylactic administration of lidocaine or high-dose amiodarone for the prevention of VT is potentially harmful. • In patients with a wide QRS complex tachycardia of unknown origin, calcium channel blockers (e.g., verapamil and diltiazem) are potentially harmful. Recommendation for Secondary Prevention of SCD in Patients with Ischemic Heart Disease Class I recommendation • In patients with ischemic heart disease, who either survive sudden cardiac arrest (SCA) due to VT/VF or experience hemodynamically unstable VT or stable sustained VT not due to reversible causes, an implantable cardioverter-defibrillator (ICD) is recommended if meaningful survival greater than one year is expected. • Value statement: A transvenous ICD provides intermediate value in the secondary prevention of SCD particularly when the patient's risk of death due to a VA is deemed high and the risk of non-arrhythmic death (either cardiac or noncardiac) is deemed low based on the patient's burden of comorbidities and functional status. • In patients with ischemic heart disease and unexplained syncope who have inducible sustained monomorphic VT on electrophysiological study, an ICD is recommended if meaningful survival of greater than one year is expected. Recommendation for Patients with Coronary Artery Spasm Class I recommendation • In patients with VA due to coronary artery spasm, treatment with maximally tolerated doses of a calcium channel blocker and smoking cessation are indicated to reduce recurrent ischemia and VA. Class IIa recommendation • In patients resuscitated from SCA due to coronary artery spasm in whom medical therapy is ineffective or not tolerated, an ICD is reasonable if meaningful survival of greater than one year is expected. Class IIb recommendation • In patients resuscitated from SCA due to coronary artery spasm, an ICD in addition to medical therapy may be reasonable if meaningful survival of greater than one year is expected. Recommendation for Primary Prevention of SCD in Patients with Ischemic Heart Disease Class I recommendation • In patients with LVEF of 35% or less that is due to ischemic heart disease who are at least 40 days' post-MI and at least 90 days post revascularization, and with NYHA class II or III HF despite guideline-directed management and therapy

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	(GDMT), an ICD is recommended if meaningful survival of greater than one year is expected. • In patients with LVEF of 30% or less that is due to ischemic heart disease who are at least 40 days post-MI and at least 90 days post revascularization, and with NYHA class I HF despite GDMT, an ICD is recommended if meaningful survival of greater than one year is expected. • In patients with nonsustained ventricular tachycardia (NSVT) due to prior MI, LVEF of 40% or less and inducible sustained VT or VF at electrophysiological study, an ICD is recommended if meaningful survival of greater than one year is expected. Class IIa recommendation • In non-hospitalized patients with NYHA class IV symptoms who are candidates for cardiac transplantation or an LVAD, an ICD is reasonable if meaningful survival of greater than one year is expected. Class III: no benefit recommendation • An ICD is not indicated for NYHA class IV patients with medication-refractory HF who are not also candidates for cardiac transplantation, an LV assist device (LVAD), or a cardiac resynchronization therapy (CRT) defibrillator that incorporates both pacing and defibrillation capabilities. Recommendation for Treatment of Recurrent VA in Patients with Ischemic Heart Disease Class I recommendation • In patients with ischemic heart disease and recurrent VA, with significant symptoms or ICD shocks despite optimal device programming and ongoing treatment with a beta blocker, amiodarone or sotalol is useful to suppress recurrent VA. • In patients with prior MI and recurrent episodes of symptomatic sustained VT, or who present with VT storm and have failed or are intolerant of amiodarone or other antiarrhythmic medications, catheter ablation is recommended. Class IIb recommendation • In patients with ischemic heart disease and ICD shocks for sustained monomorphic VT or symptomatic sustained monomorphic VT that is recurrent, or hemodynamically tolerated, catheter ablation as first-line therapy may be considered to reduce recurrent VA. Class III: Harm recommendation • In patients with prior MI, class IC antiarrhythmic medications (e.g., flecainide and propafenone) should not be used. • In patients with incessant VT or VF, an ICD should not be implanted until sufficient control of the VA is achieved to prevent repeated ICD shocks. Class III: No Benefit recommendation • In patients with ischemic heart disease and sustained monomorphic VT, coronary revascularization alone is an ineffective therapy to prevent recurrent VT. Recommendation for Treatment of Recurrent VA in Patients with Nonischemic Cardiomyopathy (NICM) Class IIa recommendation • In patients with NICM and an ICD who experience spontaneous VA or recurrent appropriate shocks despite optimal device programming and treatment with a beta blocker, amiodarone or sotalol can be beneficial. • In patients with NICM and recurrent sustained monomorphic VT who fail or are intolerant of antiarrhythmic medications, catheter ablation can be useful for reducing recurrent VT and ICD shocks. Recommendation for Arrhythmogenic Right Ventricular Cardiomyopathy

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	Class I recommendation • In selected first-degree relatives of patients with arrhythmogenic right ventricular cardiomyopathy, clinical screening for the disease is recommended along with genetic counseling and genetic testing, if the proband has a disease causing mutation. • In patients with suspected arrhythmogenic right ventricular cardiomyopathy and VA or electrocardiographic abnormalities, cardiac MRI is useful for establishing a diagnosis and for risk stratification. • In patients with arrhythmogenic right ventricular cardiomyopathy and an additional marker of increased risk of SCD (resuscitated SCA, sustained VT, significant ventricular dysfunction with RVEF or LVEF ≤35%), an ICD is recommended if meaningful survival greater than one year is expected. • In patients with arrhythmogenic right ventricular cardiomyopathy and VA, a beta blocker is recommended. • In patients with a clinical diagnosis of arrhythmogenic right ventricular cardiomyopathy, avoiding intensive exercise is recommended. Class IIa recommendation • In patients with clinically diagnosed or suspected arrhythmogenic right ventricular cardiomyopathy, genetic counseling and genetic testing can be useful for diagnosis and for gene-specific targeted family screening. • In patients with arrhythmogenic right ventricular cardiomyopathy and syncope presumed due to VA, an ICD can be useful if meaningful survival greater than one year is expected. • In patients with clinical evidence of arrhythmogenic right ventricular cardiomyopathy but not VA, a beta blocker can be useful. • In patients with arrhythmogenic right ventricular cardiomyopathy and recurrent symptomatic sustained VT in whom a beta blocker is ineffective or not tolerated, catheter ablation with availability of a combined endocardial/epicardial approach can be beneficial. • In patients with suspected arrhythmogenic right ventricular cardiomyopathy, a signal averaged ECG can be useful for diagnosis and risk stratification. Class IIb recommendation • In asymptomatic patients with clinical evidence of arrhythmogenic right ventricular cardiomyopathy, an electrophysiological study may be considered for risk stratification. Recommendation for Long QT Syndrome Class I recommendation • In patients with long QT syndrome with a resting QTc greater than 470 ms, a beta blocker is recommended. • In high-risk patients with symptomatic long QT syndrome in whom a beta blocker is ineffective or not tolerated, intensification of therapy with additional medications (guided by consideration of the particular long QT syndrome type), left cardiac sympathetic denervation, and/or an ICD is recommended. • In patients with long QT syndrome and recurrent appropriate ICD shocks despite maximum tolerated doses of a beta blocker, intensification of medical therapy with additional medications (guided by consideration of the particular long QT syndrome type) or left cardiac sympathetic denervation, is recommended. • In patients with clinically diagnosed long QT syndrome, genetic counseling and genetic testing are recommended. Class IIa recommendation • In patients with suspected long QT syndrome, ambulatory electrocardiographic monitoring, recording the ECG lying and immediately on standing, and/or exercise treadmill testing can be useful for establishing a diagnosis and monitoring the response to therapy.

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	• In asymptomatic patients with long QT syndrome and a resting QTc less than 470 ms, chronic therapy with a beta blocker is reasonable. Class IIb recommendation • In asymptomatic patients with long QT syndrome and a resting QTc greater than 500 ms while receiving a beta blocker, intensification of therapy with medications (guided by consideration of the particular long QT syndrome type), left cardiac sympathetic denervation or an ICD may be considered. Class III: harm recommendation • In patients with long QT syndrome, QT prolonging medications are potentially harmful. Recommendation for Catecholaminergic Polymorphic Ventricular Tachycardia Class I recommendation • In patients with catecholaminergic polymorphic ventricular tachycardia, a beta blocker is recommended. • In patients with catecholaminergic polymorphic ventricular tachycardia and recurrent sustained VT or syncope, while receiving adequate or maximally tolerated beta blocker, treatment intensification with either combination medication therapy (e.g., beta blocker, flecainide), left cardiac sympathetic denervation, and/or an ICD is recommended. Class IIa recommendation • In patients with catecholaminergic polymorphic ventricular tachycardia and with clinical VT or exertional syncope, genetic counseling and genetic testing are reasonable. Recommendation for short QT Syndrome Class I recommendation • In patients with short QT syndrome who have a cardiac arrest or sustained VA, an ICD is recommended if meaningful survival greater than one year is expected. Class IIa recommendation • In patients with short QT syndrome and recurrent sustained VA, treatment with quinidine can be useful. • In patients with short QT syndrome and VT/ VF storm, isoproterenol infusion can be effective. Class IIb recommendation • In patients with short QT syndrome, genetic testing may be considered to facilitate screening of first-degree relatives. Recommendation for VA in the Structurally Normal Heart Class I recommendation • In patients with symptomatic premature ventricular complexes (PVCs) in an otherwise normal heart, treatment with a beta blocker or nondihydropyridine calcium channel blocker is useful to reduce recurrent arrhythmias and improve symptoms. Class IIa recommendation • In patients with symptomatic VA in an otherwise normal heart, treatment with an antiarrhythmic medication is reasonable to reduce recurrent symptomatic arrhythmias and improve symptoms if beta blockers and nondihydropyridine calcium channel blockers are ineffective or not tolerated. Recommendation for Outflow Tract VA Class I recommendation • In patients with symptomatic outflow tract VA in an otherwise normal heart for whom antiarrhythmic medications are ineffective, not tolerated, or not the patient's preference, catheter ablation is useful.

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	• In patients with symptomatic outflow tract VT in an otherwise normal heart, a beta blocker or a calcium channel blocker is useful. Recommendation for PVC-Induced Cardiomyopathy Class I recommendation • For patients who require arrhythmia suppression for symptoms or declining ventricular function suspected to be due to frequent PVCs (generally >15% of beats and predominately of 1 morphology) and for whom antiarrhythmic medications are ineffective, not tolerated, or not the patient's preference, catheter ablation is useful. Class IIa recommendation • In patients with PVC-induced cardiomyopathy, pharmacological treatment (e.g., beta blocker, amiodarone) is reasonable to reduce recurrent arrhythmias and improve symptoms and LV function. Recommendation for Pregnancy Class I recommendation • In mothers with long QT syndrome, a beta blocker should be continued during pregnancy and throughout the postpartum period including in women who are breastfeeding. • In the pregnant patient with sustained VA, electrical cardioversion is safe and effective and should be used with standard electrode configuration. Class IIa recommendation • In pregnant patients needing an ICD or VT ablation, it is reasonable to undergo these procedures during pregnancy, preferably after the first trimester. Recommendation for Medication-Induced Arrhythmias Class I recommendation • Administration of digoxin antibodies is recommended for patients who present with sustained VA potentially due to digoxin toxicity. • In patients with recurrent torsades de pointes associated with acquired QT prolongation and bradycardia that cannot be suppressed with intravenous magnesium administration, increasing the heart rate with atrial or ventricular pacing or isoproterenol are recommended to suppress the arrhythmia. • For patients with QT prolongation due to a medication, hypokalemia, hypomagnesemia, or other acquired factor and recurrent torsades de pointes, administration of intravenous magnesium sulfate is recommended to suppress the arrhythmia. • For patients with torsades de pointes associated with acquired QT prolongation, potassium repletion to 4.0 mmol/L or more and magnesium repletion to normal values (e.g., ≥2.0 mmol/L) are beneficial. Class IIa recommendation • In patients taking sodium channel blockers who present with elevated defibrillation or pacing thresholds, discontinuing the presumed responsible medication or reprogramming the device can be useful to restore effective device therapy. Class III: harm recommendation • In patients with congenital or acquired long QT syndrome, QT-prolonging medications are potentially harmful.
European Society of Cardiology: **Guidelines for the management of cardiomyopathies (2023)**[20]	Recommendations for management of atrial fibrillation and atrial flutter in patients with cardiomyopathy • Anticoagulation ○ Oral anticoagulation in order to reduce the risk of stroke and thromboembolic events is recommended in all patients with hypertrophic cardiomyopathy or cardiac amyloidosis and atrial fibrillation (AF) or atrial flutter (unless

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	contraindicated). ○ Oral anticoagulation to reduce the risk of stroke and thrombo-embolic events is recommended in patients with dilated cardiomyopathy, non-dilated left ventricular cardiomyopathy, or arrhythmogenic right ventricular cardiomyopathy, and AF or atrial flutter with a CHA2DS2-VASc score ≥2 in men or ≥3 in women. • Control of symptoms and heart failure ○ Atrial fibrillation catheter ablation is recommended for rhythm control after one failed or intolerant class I or III antiarrhythmic drug to improve symptoms of AF recurrences in patients with paroxysmal or persistent AF and cardiomyopathy. ○ Atrial fibrillation catheter ablation is recommended to reverse, left ventricular dysfunction in AF patients with cardiomyopathy when a tachycardia-induced component is highly probable, independent of their symptom status. • Comorbidities and associated risk factor management ○ Modification of an unhealthy lifestyle and targeted therapy of intercurrent conditions is recommended to reduce AF burden and symptom severity in patients with cardiomyopathy. <u>Recommendations for medical treatment of left ventricular outflow tract obstruction</u> • Non-vasodilating beta-blockers, titrated to maximum tolerated dose, are recommended as first-line therapy to improve symptoms in patients with resting or provoked left ventricular outflow tract (LVOTO). • Verapamil or diltiazem, titrated to maximum tolerated dose, are recommended to improve symptoms in symptomatic patients with resting or provoked LVOTO who are intolerant or have contraindications to beta-blockers. • Disopyramide, titrated to maximum tolerated dose, is recommended in addition to a beta-blocker (or, if this is not possible, with verapamil or diltiazem) to improve symptoms in patients with resting or provoked LVOTO.
Eighth Joint National Committee (JNC 8): **2014 Evidence-based Guideline for the Management of High Blood Pressure in Adults (2014)**[21]	• Pharmacologic treatment should be initiated in patients ≥60 years of age to lower blood pressure at systolic blood pressure ≥150 mm Hg or diastolic blood pressure ≥90 mm Hg and to a goal systolic blood pressure <150 mm Hg and goal diastolic blood pressure <90 mm Hg. Adjustment of treatment is not necessary if treatment results in lower blood pressure and treatment is well tolerated and without adverse effects on health or quality of life. • In patients <60 years of age, pharmacologic treatment should be initiated to lower blood pressure at diastolic blood pressure ≥90 mm Hg to a goal diastolic blood pressure <90 mm Hg. • In patients <60 years of age, pharmacologic treatment should be initiated to lower blood pressure at systolic blood pressure ≥150 mm Hg to a goal diastolic blood pressure <140 mm Hg. • For patients ≥18 years of age with chronic kidney disease or diabetes, pharmacologic treatment should be initiated to lower blood pressure at systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg and to a goal systolic blood pressure <140 mm Hg and goal diastolic blood pressure <90 mm Hg. • Initial antihypertensive treatment for the general nonblack population, including those with diabetes, should include thiazide-type diuretic, calcium channel blocker (CCB), ACE inhibitor, or ARB. • Initial antihypertensive treatment for the general black population, including those with diabetes, should include thiazide-type diuretic or CCB. • For patients ≥18 years of age with chronic kidney disease regardless of race or diabetes status, initial (or add-on) treatment should include an ACE inhibitor or ARB to improve kidney outcomes. • The main goal of antihypertensive treatment is to attain and maintain goal blood

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	pressure. • If goal blood pressure is not attained within a month of treatment, the dose of the initial drug should be increased or second drug from the thiazide-type diuretic, CCB, ACE inhibitor, or ARB classes should be added. • If goal is not achieved with two drugs, a third drug from the thiazide-type diuretic, CCB, ACE inhibitor, or ARB classes should be added. • An ACE inhibitor and ARB should not be used together. • Antihypertensive classes can be used if the patient is unable to achieve goal blood pressure with three agents or had a contraindication to a preferred class. • If blood pressure is not able to be achieved or in complicated patients, referral to a hypertension specialist may be indicated.
International Society of Hypertension: **Global Hypertension Practice Guidelines (2020)**[22]	<u>Lifestyle modifications</u> • Lifestyle modification is the first line of antihypertensive treatment. • Salt reduction: Reduce salt added when preparing foods, and at the table. Avoid or limit consumption of high salt foods such as soy sauce, fast foods and processed food including breads and cereals high in salt. • Healthy diet: Eating a diet that is rich in whole grains, fruits, vegetables, polyunsaturated fats and dairy products and reducing food high in sugar, saturated fat and trans fats, such as the DASH diet. • Healthy drinks: Moderate consumption of coffee, green and black tea. Other beverages that can be beneficial include karkadé (hibiscus) tea, pomegranate juice, beetroot juice and cocoa. • Moderation of alcohol consumption: The recommended daily limit for alcohol consumptions is two standard drinks for men and 1.5 for women (10 g alcohol/standard drink). Avoid binge drinking. • Weight reduction: Body weight control is indicated to avoid obesity. Particularly abdominal obesity should be managed. Ethnic-specific cut-offs for BMI and waist circumference should be used. Alternatively, a waist-to-height ratio <0.5 is recommended for all populations. • Smoking cessation: Smoking is a major risk factor for cardiovascular disease (CVD), COPD and cancer. Smoking cessation and referral to smoking cessation programs are advised. • Regular physical activity: Studies suggest that regular aerobic and resistance exercise may be beneficial for both the prevention and treatment of hypertension. Moderate intensity aerobic exercise (walking, jogging, cycling, yoga, or swimming) for 30 minutes on five to seven days per week Strength training also can help reduce blood pressure. Performance of resistance/strength exercises on two to three days per week. • Reduce stress and induce mindfulness: Stress should be reduced and mindfulness or meditation introduced into the daily routine. • Reduce exposure to air pollution and cold temperature: Evidence from studies support a negative effect of air pollution on blood pressure in the long-term. <u>Pharmacological Treatment</u> • Ideal characteristics of drug treatment o Treatments should be evidence-based in relation to morbidity/mortality prevention. o Use a once-daily regimen which provides 24-hour blood pressure control. o Treatment should be affordable and/or cost-effective relative to other agents. o Treatments should be well-tolerated. o Evidence of benefits of use of the medication in populations to which it is to be applied. • General scheme for drug treatment o Lifestyle modification is the first line of antihypertensive treatment.

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	○ Grade 1 hypertension (BP 140 to 159/ 90 to 99): Immediate drug treatment in high-risk patients or those with CVD, chronic kidney disease (CKD), diabetes mellitus (DM), or hypertension-mediated organ damage (HMOD). Drug treatment after three to six months of lifestyle intervention if BP still not controlled in low to moderate risk patients. ○ Grade 2 hypertension (BP ≥160/100): Immediate drug treatment in all patients. • Core drug-treatment strategy ○ Step 1: Dual low-dose combination (ACE inhibitor or ARB plus dihydropyridine-calcium channel blockers (DHP-CCB)); consider monotherapy in low-risk grade 1 hypertension or in very old (≥80 years) or frail patients; consider ACE/ARB plus thiazide-like diuretic in post-stroke, very elderly, incipient HF, or CCB intolerance; consider ACE/ARB plus DHP-CCB or DHP-CCB plus thiazide-like diuretics in black patients. ○ Step 2: Dual full-dose combination (ACE inhibitor or ARB plus DHP-CCB); consider monotherapy in low-risk grade 1 hypertension or in very old (≥80 years) or frail patients; consider ACE/ARB plus thiazide-like diuretic in post-stroke, very elderly, incipient HF, or CCB intolerance. ○ Step 3: Triple combination (ACE/ARB plus DHP-CCB plus thiazide-like diuretic). ○ Step 4, resistant hypertension: triple combination plus spironolactone or other drug, alternatives include amiloride, doxazosin, eplerenone, clonidine, or β-blocker. Caution with spironolactone or other potassium sparing diuretics when estimated GFR <45 mL/min/1.73m^2 or K+ >4.5 mmol/L. ○ Consider β-blockers at any treatment step when there is a specific indications for their use, e.g., heart failure, angina, post-MI, atrial fibrillation, or younger women planning pregnancy or pregnant.
Hypertension Canada: **2020 Guidelines for the Prevention, Diagnosis, Risk Assessment, and Treatment of Hypertension in Adults and Children (2020)[23]**	<u>Indications for drug therapy for adults with hypertension without compelling indications for specific agents</u> • Antihypertensive therapy should be prescribed for average diastolic blood pressure (DBP) measurements of ≥100 mmHg or average systolic blood pressure (SBP) measurements of ≥160 mmHg in patients without macrovascular target organ damage or other cardiovascular risk factors. • Antihypertensive therapy should be strongly considered for average DPB readings ≥90 mmHg or for average SBP readings ≥140 mmHg in the presence of macrovascular target organ damage or other independent cardiovascular risk factors. • For high-risk patients, aged 50 years or older, with SBP levels ≥130 mmHg, intensive management to target a SBP <120 mmHg should be considered. Patient selection for intensive management is recommended and caution should be taken in certain high-risk groups. <u>Indications for drug therapy for adults with diastolic and with or without systolic hypertension</u> • Initial therapy should be with either monotherapy or single pill combination (SPC). ○ Recommended monotherapy choices are: ▪ A thiazide/thiazide-like diuretic, with longer-acting diuretics preferred; ▪ A β-blocker (in patients <60 years of age); ▪ An angiotensin-converting enzyme (ACE) inhibitor (in nonblack patients); ▪ An angiotensin receptor blocker (ARB); or

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	▪ A long-acting calcium channel blocker (CCB). o Recommended SPC choices are those in which an ACE inhibitor is combined with a CCB, ARB with a CCB, or ACE inhibitor or ARB with a diuretic. o Hypokalemia should be avoided in patients treated with thiazide/thiazide-like diuretic monotherapy. • Additional antihypertensive drugs should be used if target BP levels are not achieved with standard-dose monotherapy. Add-on drugs should be chosen from first-line choices. Useful choices include a thiazide/thiazide-like diuretic or CCB with either: ACE inhibitor, ARB, or β-blocker. Caution should be exercised in combining a nondihydropyridine CCB and a β-blocker. The combination of an ACE inhibitor and an ARB is not recommended. • If BP is still not controlled with a combination of two or more first-line agents, or there are adverse effects, other antihypertensive drugs may be added. • Possible reasons for poor response to therapy should be considered. • α-Blockers are not recommended as first-line agents for uncomplicated hypertension; β-blockers are not recommended as first-line therapy for uncomplicated hypertension in patients ≥60 years of age; and ACE inhibitors are not recommended as first-line therapy for uncomplicated hypertension in black patients. However, these agents may be used in patients with certain comorbid conditions or in combination therapy. <u>Indications for drug therapy for adults with isolated systolic hypertension</u> • Initial therapy should be single-agent therapy with a thiazide/thiazide-like diuretic, a long-acting dihydropyridine CCB, or an ARB. If there are adverse effects, another drug from this group should be substituted. Hypokalemia should be avoided in patients treated with thiazide/thiazide-like diuretic monotherapy. • Additional antihypertensive drugs should be used if target BP levels are not achieved with standard-dose monotherapy. Add-on drugs should be chosen from first-line options. • If BP is still not controlled with a combination of two or more first-line agents, or there are adverse effects, other classes of drugs (such as α-blockers, ACE inhibitors, centrally acting agents, or nondihydropyridine CCBs) may be combined or substituted. • Possible reasons for poor response to therapy should be considered. • α-Blockers are not recommended as first-line agents for uncomplicated isolated systolic hypertension; and β-blockers are not recommended as first-line therapy for isolated systolic hypertension in patients ≥60 years of age. However, both agents may be used in patients with certain comorbid conditions or in combination therapy. <u>Guidelines for hypertensive patients with coronary artery disease (CAD)</u> • For most hypertensive patients with CAD, an ACE inhibitor or ARB is recommended. • For hypertensive patients with CAD, but without coexisting systolic heart failure, the combination of an ACE inhibitor and ARB is not recommended. • For high-risk hypertensive patients, when combination therapy is being used, choices should be individualized. The combination of an ACE inhibitor and a dihydropyridine CCB is preferable to an ACE inhibitor and a thiazide/thiazide-like diuretic in selected patients. • For patients with stable angina pectoris but without previous heart failure, myocardial infarction, or coronary artery bypass surgery, either a β-blocker or CCB can be used as initial therapy. • Short-acting nifedipine should not be used. • When decreasing SBP to target levels in patients with established CAD (especially if isolated systolic hypertension is present), be cautious when the DBP is ≤60

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	mmHg because of concerns that myocardial ischemia might be exacerbated, especially in patients with left ventricular hypertrophy (LVH).
	
	<u>Guidelines for patients with hypertension who have had a recent myocardial infarction</u>
	• Initial therapy should include a β-blocker as well as an ACE inhibitor.
	• An ARB can be used if the patient is intolerant of an ACE inhibitor.
	• CCBs may be used in patients after myocardial infarction when β-blockers are contraindicated or not effective. Nondihydropyridine CCBs should not be used when there is heart failure, evidenced by pulmonary congestion on examination or radiography.
	
	<u>Treatment of hypertension in association with heart failure</u>
	• In patients with systolic dysfunction (ejection fraction <40%), ACE inhibitors and β-blockers are recommended for initial therapy. Aldosterone antagonists (mineralocorticoid receptor antagonists) may be combined in treatment for patients with a recent cardiovascular hospitalization, acute myocardial infarction, elevated B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide level, or New York Heart Association (NYHA) Class II-IV symptoms. Careful monitoring for hyperkalemia is recommended when combining an aldosterone antagonist with ACE inhibitor or ARB treatment. Other diuretics are recommended as additional therapy if needed. Beyond considerations of BP control, doses of ACE inhibitors or ARBs should be titrated to those reported to be effective in trials unless adverse effects become manifest.
	• An ARB is recommended if ACE inhibitors are not tolerated.
	• A combination of hydralazine and isosorbide dinitrate is recommended if ACE inhibitors and ARBs are contraindicated or not tolerated.
	• For hypertensive patients whose BP is not controlled, an ARB may be combined with an ACE inhibitor and other antihypertensive drug treatment. Careful monitoring should be used if combining an ACE inhibitor and an ARB because of potential adverse effects such as hypotension, hyperkalemia, and worsening renal function. Additional therapies may also include dihydropyridine CCBs.
	• An angiotensin receptor-neprilysin inhibitor (ARNI) should be used in place of an ACE inhibitor or ARB for patients with HFrEF (<40%) who remain symptomatic despite treatment with appropriate dose of guideline directed HF therapy. Eligible patients must have a serum potassium <5.2 mmol/L, an eGFR ≤30 mL/min/1.73m^2 and close surveillance of serum potassium and creatinine.
	
	<u>Treatment of hypertension in association with stroke</u>
	• BP management in acute ischemic stroke (onset to 72 hours)
	  o Please refer to Stroke Best Practice recommendations.
	• BP management after acute ischemic stroke
	  o Strong consideration should be given to the initiation of antihypertensive therapy after the acute phase of a stroke or transient ischemic attack.
	  o After the acute phase of a stroke, BP-lowering treatment is recommended to a target of consistently <140/90 mmHg.
	  o Treatment with an ACE inhibitor and thiazide/thiazide-like diuretic combination is preferred.
	  o For patients with stroke, the combination of an ACE inhibitor and ARB is not recommended.
	• BP management in hemorrhagic stroke (onset to 72 hours)
	  o Please refer to Stroke Best Practice recommendations.
	
	<u>Treatment of hypertension in association with LVH</u>
	• Hypertensive patients with LVH should be treated with antihypertensive therapy to decrease the rate of subsequent cardiovascular events.

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	• The choice of initial therapy can be influenced by the presence of LVH. Initial therapy can be drug treatment using ACE inhibitors, ARBs, long-acting CCBs, or thiazide/thiazide-like diuretics. Direct arterial vasodilators such as hydralazine or minoxidil should not be used. <u>Treatment of hypertension in association with nondiabetic chronic kidney disease</u> • Individualize BP targets in patients with chronic kidney disease. Consider intensive targets (SBP <120 mmHg) in appropriate patients. • For patients with hypertension and proteinuric chronic kidney disease (urinary protein >150 mg per 24 hours or albumin to creatinine ratio >30 mg/mmol), initial therapy should be an ACE inhibitor or an ARB if there is intolerance to ACE inhibitors. • In most cases, combination therapy with other antihypertensive agents might be needed to reach target BP levels. • The combination of an ACE inhibitor and ARB is not recommended for patients with nonproteinuric chronic kidney disease. <u>Treatment of hypertension in association with renovascular disease</u> • Patients with hypertension attributable to atherosclerotic renal artery stenosis should be primarily medically managed because renal angioplasty and stenting offers no benefit over optimal medical therapy alone. • Renal artery angioplasty and stenting for atherosclerotic hemodynamically significant renal artery stenosis could be considered for patients with uncontrolled hypertension resistant to maximally tolerated pharmacotherapy, progressive renal function loss, and acute pulmonary edema. • Patients with confirmed renal fibromuscular dysplasia (FMD) should be referred to a hypertension specialist. • Renal artery angioplasty without stenting is recommended for treatment of FMD-related renal artery stenosis. Stenting is not recommended unless needed because of a periprocedural dissection. Surgical revascularization should be considered in cases of complex lesions less amendable to angioplasty, stenosis associated with complex aneurysm, and restenosis despite two unsuccessful attempts of angioplasty. <u>Treatment of hypertension in association with diabetes mellitus</u> • Persons with diabetes mellitus should be treated to attain SBP of <130 mmHg and DBP of <80 mmHg. • For persons with cardiovascular or kidney disease, including microalbuminuria, or with cardiovascular risk factors in addition to diabetes and hypertension, an ACE inhibitor or an ARB is recommended as initial therapy. • For persons with diabetes and hypertension not included in other guidelines in this section, appropriate choices include (in alphabetical order): ACE inhibitors, ARBs, dihydropyridine CCBs, and thiazide/thiazide-like diuretics. • If target BP levels are not achieved with standard-dose monotherapy, additional antihypertensive therapy should be used. For persons in whom combination therapy with an ACE inhibitor is being considered, a dihydropyridine CCB is preferable to a thiazide/thiazide-like diuretic. <u>Resistant hypertension</u> • Resistant hypertension is defined as BP above target despite three or more BP-lowering drugs at optimal doses preferably including a diuretic (and usually a renin-angiotensin-aldosterone system blocker and a CCB. • Accurate office and out-of-office BP measurement is essential. • Other reasons for apparent resistant hypertension should be eliminated before diagnosing true resistant hypertension, including nonadherence, white coat effect,

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	and secondary hypertension. • Pharmacotherapy with the additional use of spironolactone, bisoprolol, doxazosin, amiloride, eplerenone, or clonidine with the baseline regimen decreases BP significantly, with the greatest BP-lowering shown with spironolactone. • Patients with resistant hypertension should be referred to providers with expertise in diagnosis and management of hypertension. Hypertension and pediatrics • BP should be measured regularly in children three years of age or older; the auscultatory method is the gold-standard at present. • Initial therapy should be monotherapy, with an ACE inhibitor or ARB (not first-line in black children), or a long-acting dihydropyridine CCB. • The treatment t goal is systolic and diastolic office BP and/or ABPM < 95th percentile or <90th percentile in children with risk factors or target organ damage. • Complex cases should be referred to an expert in pediatric hypertension. Hypertension and pregnancy • Up to 7% of pregnancies are complicated by a hypertensive disorder of pregnancy, and approximately 5% of women will have chronic hypertension when they become pregnant. • The prevalence of hypertension in pregnancy is expected to increase with women becoming pregnant later in their reproductive years and the increasing prevalence of cardiovascular comorbidities such as increased preconception body mass index and maternal diabetes. • The possibility of pregnancy should be considered when managing women with hypertension who are of reproductive age. • Preconception counselling should be offered to all women with hypertension who are considering pregnancy. • ACE inhibitor and ARB therapy should be avoided before conception and during pregnancy unless there is a compelling indication for their use (i.e., proteinuric kidney disease). • Hypertension during pregnancy can increase the risk of adverse maternal and fetal outcomes, including an increased risk of preeclampsia, placental abruption, prematurity, small for gestational age infants, stillbirth, and maternal renal and retinal injury, thus generally requires involvement of an interdisciplinary team including obstetrical care providers. • Antihypertensive therapy is recommended for average SBP measurements of ≥140 mmHg or DBP measurements of ≥90 mmHg in pregnant women with chronic hypertension, gestational hypertension, or preeclampsia. Initial antihypertensive therapy should be monotherapy from the following first-line drugs: oral labetalol, oral methyldopa, long-acting oral nifedipine, or other oral b-blockers (acebutolol, metoprolol, pindolol, and propranolol). Other antihypertensive drugs can be considered as second-line drugs including: clonidine, hydralazine, and thiazide diuretics. • Women with severe hypertension with SBP ≥160 mmHg or DBP ≥110 mmHg in pregnancy or postpartum require urgent antihypertensive therapy because it is considered an obstetrical emergency. • Antihypertensive drugs used in breastfeeding women include: labetalol, methyldopa, long-acting nifedipine, enalapril, or captopril.
European Society of Hypertension: **2023 Guidelines for the management of arterial hypertension**	General recommendations for antihypertensive drug treatment • BP lowering should be prioritized over the selection of specific antihypertensive drug classes because treatment benefit largely originates from BP reduction. • Five major drug classes including, ACE inhibitors, ARBs, β-blockers, CCBs, and Thiazide/Thiazide-like diuretics have effectively reduced blood pressure and cardiovascular events in randomized controlled trials. These drugs and their

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(2023)[24]	combinations are recommended as the basis of antihypertensive treatment strategies. • Initiation of therapy with a two-drug combination is recommended for most hypertensive patients. Preferred combinations should comprise a RAS blocker (either an ACE inhibitor or an ARB) with a CCB or thiazide/thiazide-like diuretic. Other combinations of the five major drug classes can be used. • Initiation with monotherapy can be considered in patients with: grade 1 hypertension and low-risk if BP is only marginally elevated (less than 150 mmHg SBP and 95 mmHg DBP) high-normal BP and very high cardiovascular risk, frailty and/or and advance age. • If BP is not controlled with the initial two-drug combination by using the maximum recommended and tolerated dose of the respective components, treatment should be increased to a three-drug combination, usually a RAS blocker plus CCB plus thiazide/thiazide-like diuretic. • If BP is not controlled with a three-drug combination by using the maximum recommended and tolerated dose of the respective components, it is recommended to extend treatment according to the recommendations for resistant hypertension. • The use of single pill combinations should be preferred at any treatment step (i.e. during initiation of therapy with a two-drug combination and at any other step of treatment). • β-blocker should be used at initiation of therapy or at any treatment step as guideline-directed medical therapy (e.g., heart failure with reduced ejection fraction, anti-ischemic therapy in chronic coronary syndromes, heart rate control in atrial fibrillation). • β-blockers can be considered in the presence of several other conditions in which their use can be favorable. • The combination of two RAS blockers is not recommended due to increased risk of adverse events, in particular AKI. True-resistant hypertension • In resistant hypertension, it is recommended to reinforce lifestyle measures. • Drugs that can be considered as additional therapy in patients with resistant hypertension are preferably spironolactone (or other MRA), or β-blocker or Alpha-1 blockers or centrally acting agents (clonidine), or amiloride. • Thiazide/thiazide-like diuretics are recommended in resistant hypertension if estimated eGFR is ≥30 mL/min/1.73m^2. • Loop diuretics may be considered in patients with an estimated eGFR < 45 mL/min/1.73m^2 and should be used if eGFR falls below 30 mL/min/1.73m^2. • Chlorthalidone (12.5 to 25 mg once daily) could be used with or without a loop diuretic if eGFR is <30 mL/min/1.73m^2. • Renal deprivation can be considered as an additional treatment option in patients with resistant hypertension if eGFR is >40 mL/min/1.73m^2. • Patients with resistant hypertension should be followed very closely. Follow-up includes periodical ambulatory blood pressure monitoring and assessment of hypertension-mediated organ damage, particularly kidney function and serum potassium levels. Regular use of home blood pressure monitoring and monitoring of drug adherence are desirable.
National Institute for Health and Clinical Excellence: **Hypertension in adults: diagnosis and management (2019)[25]**	Choosing antihypertensive drug treatment (for people with or without type II diabetes) • Where possible, recommend treatment with drugs taken only once a day. • Prescribe non-proprietary drugs where these are appropriate and minimize cost. • Offer people with isolated systolic hypertension (systolic blood pressure ≥160 mmHg) the same treatment as people with both raised systolic and diastolic blood pressure. • Offer antihypertensive drug treatment to women of child-bearing potential with diagnosed hypertension in line with recommendations in this guideline. For

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	women considering pregnancy or who are pregnant or breastfeeding, manage hypertension in line with the recommendations on Management of pregnancy with chronic hypertension and Breastfeeding in 'Hypertension in pregnancy'. • When choosing antihypertensive drug treatment for adults of black African or African-Caribbean family origin, consider an angiotensin II receptor blocker, in preference to an angiotensin-converting enzyme inhibitor. <u>Step one treatment</u> • Patients <55 years of age should be offered a step one antihypertensive with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). • Offer an ACE inhibitor or an ARB to adults starting step 1 antihypertensive treatment who have type II diabetes and are of any age or family origin or those aged <55 years but not of black African or African-Caribbean family origin. • If an ACE inhibitor is not tolerated, offer an ARB. • Do not combine an ACE inhibitor with an ARB for the treatment of hypertension. • Offer a calcium channel blocker (CCB) to adults starting step 1 antihypertensive treatment who are >55 years of age and do not have diabetes and are of black African or African-Caribbean family origin and do not have type II diabetes and of any age. • If a CCB is not suitable, for example because of edema or intolerance, or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic. • If diuretic treatment is to be initiated or changed, offer a thiazide‑like diuretic, such as indapamide in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide. • For adults with hypertension who are already receiving treatment with bendroflumethiazide or hydrochlorothiazide, who have stable, well-controlled blood pressure, continue with their treatment. <u>Step two treatment</u> • Before considering next step treatment for hypertension discuss with the person if they are taking their medicine as prescribed and support adherence in line with NICE's guideline on “Medicines adherence: involving patients decisions about prescribed medicines and supporting adherence”. • If hypertension is not controlled with a step one treatment of an ACE inhibitor or ARB, offer choice of one of the following drugs in addition to the step one treatment: a CCB or a thiazide-like diuretic. • If hypertension is not controlled in adults taking step one treatment of a CCB, offer the choice of one of the following drugs in addition to the step one treatment: an ACE inhibitor or an ARB or a thiazide-like diuretic. • If hypertension is not controlled in adults of black African or African–Caribbean family origin who do not have type 2 diabetes taking step one treatment, consider an ARB, in preference to an ACE inhibitor, in addition to step one treatment. <u>Step three treatment</u> • Before considering step three treatment, review the person’s medications to ensure they are being taken at the optimal doses and discuss adherence (see recommendation under step two). • If hypertension is not controlled in adults taking step two treatment, offer a combination of an ACE inhibitor or ARB and a CCB and a thiazide-like diuretic. <u>Step four treatment</u> • If hypertension is not controlled in adults taking the optimal tolerated doses of an ACE inhibitor or an ARB plus a CCB and a thiazide-like diuretic, regard them as

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	having resistant hypertension. • Before considering further treatment for a person with resistant hypertension, confirm elevated clinic blood pressure measurements using ambulatory or home blood pressure recordings, assess for postural hypotension, and discuss adherence. • For people with confirmed resistant hypertension, consider adding a fourth antihypertensive drug as step four treatment or seeking specialist advice. • Consider further diuretic therapy with low-dose spironolactone for adults with resistant hypertension starting step four treatment who have a blood potassium level of 4.5 mmol/l or less. Use particular caution in people with a reduced estimated glomerular filtration rate because they have an increased risk of hyperkalemia. • When using further diuretic therapy for step four treatment of resistant hypertension, monitor blood sodium and potassium and renal function within one month of starting treatment and repeat as needed thereafter. • Consider an alpha-blocker or beta-blocker for adults with resistant hypertension starting step four treatment who have a blood potassium level of more than 4.5 mmol/l. • If blood pressure remains uncontrolled in people with resistant hypertension taking the optimal tolerated doses of four drugs, seek specialist advice.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in Blacks (2010)**[26]	• To attain and maintain blood pressure (BP) below target levels, multiple antihypertensive drugs will be required in most hypertensive blacks. • Use of two-drug combination therapy when SBP is >15 mm Hg and/or DBP is >10 mm Hg above goal levels is increasingly recommended as first-line therapy. • Two-drug regimens have generally contained a thiazide-type diuretic; however, the combination of a calcium channel blocker (CCB) with either an ACE inhibitor or an ARB has been shown equally efficacious in BP lowering but with demonstrated superiority (CCB+ACE) for hard clinical outcomes compared with the same ACE inhibitor plus a thiazide-type diuretic. • In secondary prevention patients, the combination therapy should include a drug(s) with the appropriate compelling indications. • Certain classes of antihypertensive medications, specifically diuretics and CCBs, lower BP on average more than β-blockers and renin-angiotensin system (RAS) blockers in black patients when used as monotherapies. • In the absence of compelling indications, when BP is near goal levels, monotherapy with a diuretic or a CCB is preferred. • Lifestyle modifications should be initiated in all patients with hypertension, whether or not pharmacotherapy is planned. • ACE inhibitors or ARBs are recommended as alternative monotherapy options in the treatment of hypertension in blacks. The rationale for their lower tier monotherapy recommendation is because they have consistently achieved lesser average reductions in BP relative to that observed with monotherapy using either a diuretic or CCB.
Kidney Disease Improving Clinical Outcomes Group: **KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease (2021)**[27]	<u>Blood pressure measurement</u> • The Work Group recommends standardized office blood pressure (BP) measurement in preference to routine office BP measurements for the management of high BP in adults. • The Work Group suggests that out-of-office BP measurements with ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM) be used to complement standardized office BP readings for the management of high BP. <u>Lifestyle interventions for lowering BP in patients with chronic kidney disease (CKD) not receiving dialysis</u> • The Work Group suggests targeting a sodium intake <2 grams of sodium per day (or <90 mmol of sodium per day, or <5 grams of sodium chloride per day) in

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	patients with high BP and CKD. • The Work Group suggests that patients with high BP and CKD be advised to undertake moderate-intensity physical activity for a cumulative duration of at least 150 minutes per week, or to a level compatible with their cardiovascular and physical tolerance. <u>BP management in patients with CKD, with or without diabetes, not receiving dialysis</u> • The Work Group suggests that adults with high BP and CKD be treated with a target systolic BP (SBP) of <120 mmHg, when tolerated, using standardized office BP measurement. • The Work Group recommends starting renin-angiotensin-system inhibitors (RASi) (angiotensin-converting enzyme inhibitor [ACEi] or angiotensin II receptor blocker [ARB]) for people with high BP, CKD, and severely increased albuminuria without diabetes. • The Work Group suggests starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately increased albuminuria without diabetes. • The Work Group recommends starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately-to-severely increased albuminuria with diabetes. • The Work Group recommends avoiding any combination of ACEi, ARB, and direct renin inhibitor (DRI) therapy in patients with CKD, with or without diabetes. <u>BP management in kidney transplant recipients</u> • Treat adult kidney transplant recipients with high BP to a target BP of <130 mmHg systolic and <80 mmHg diastolic using standardized office BP measurement. • The Work Group recommends that a dihydropyridine calcium channel blocker (CCB) or an ARB be used as the first-line antihypertensive agent in adult kidney transplant recipients. <u>BP management in children with CKD</u> • The Work Group suggests that in children with CKD, 24-hour mean arterial pressure by ABPM should be lowered to <50th percentile for age, sex, and height.
American College of Cardiology/ American Heart Association Task Force: **Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults (2017)**[28]	<u>Initiation of Blood Pressure (BP) Treatment for Overall Cardiovascular Disease (CVD) Risk</u> • Use of BP-lowering medications is recommended for secondary prevention of recurrent CVD events in patients with clinical CVD and an average systolic blood pressure (SBP) ≥130 mmHg or an average diastolic blood pressure (DBP) of ≥80 mmHg and for primary prevention in adults with an estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk of ≥10% and an average SBP of ≥130 mmHg or an average ≥80 mmHg. • Use of BP-lowering medication is recommended for primary prevention of CVD in adults with no history of CVD and with an estimated 10-year ASCVD risk <10% and an SBP of ≥140 mmHg or a DBP of ≥90 mmHg. • Simultaneous use of an angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), and/or renin inhibitor is potentially harmful and is not recommended to treat adults with hypertension. • For adults with confirmed hypertension and known CVD or 10-year ASCVD risk of ≥10%, a BP target <130/80 mmHg is recommended. For adults with confirmed hypertension without additional markers of increased CVD risk, a BP target <130/80 mmHg may be reasonable. • For initiation of antihypertensive drug therapy, first-line agents include thiazide diuretics, calcium channel blockers (CCBs), and ACE inhibitors or ARBs. • Initiation of antihypertensive drug therapy with two first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended

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	in adults with stage 2 hypertension and an average BP >20/10 mmHg above their BP target. • Initiation of antihypertensive drug therapy with a single antihypertensive drug is reasonable in adults with stage 1 hypertension and BP goal <130/80 mmHg with dosage titration and sequential addition of other agents to achieve the BP target. Stable Ischemic Heart Disease (SIHD) • In adults with SIHD and hypertension, a BP target <130/80 is recommended. • Adults with SIHD and hypertension (BP ≥130/80 mmHg) should be treated with medications [e.g., guideline-directed medical therapy (GDMT) beta-blockers, ACE inhibitors, or ARBs] for compelling indications [e.g., previous myocardial infarction (MI), stable angina] as first-line therapy, with the addition of other drugs (e.g., dihydropyridine CCBs, thiazide diuretics, and/or mineralocorticoid receptor antagonists) as needed to further control hypertension. • In adults with SIHD with angina and persistent uncontrolled hypertension, the addition of dihydropyridine CCBs to GDMT beta-blockers is recommended. • In adults who have had a MI or acute coronary syndrome, it is reasonable to continue GDMT beta-blockers beyond three years as long-term therapy for hypertension. • Beta-blockers and/or CCBs might be considered to control hypertension in patients with coronary artery disease (CAD) had an MI more than three years ago and have angina. Heart Failure • In adults with increased risk of HF, the optimal BP in those with hypertension should be <130 mmHg. • Adults with HFrEF and hypertension should be prescribed GDMT titrated to attain a BP <130/80 mmHg. • Non-dihydropyridine CCBs are not recommended in the treatment of hypertension in adults with HFrEF. • In adults with HFpEF who present with symptoms of volume overload, diuretics should be prescribed to control hypertension. • Adults with HFpEF and persistent hypertension after management of volume overload should be prescribed ACE inhibitors or ARBs and beta-blockers titrated to attain SBP <130 mmHg. CKD • Adults with hypertension and CKD should be treated to a BP goal <130/80 mmHg. • In adults with hypertension and CKD [stage 3 or higher or stage 1 or 2 with albuminuria (≥300 mg/d, or ≥300 mg/g albumin-to-creatinine ratio or the equivalent in the first morning void)], treatment with an ACE inhibitor is reasonable to slow kidney disease progression. Treatment with an ARB may be reasonable if an ACE inhibitor is not tolerated. • After kidney transplantation, it is reasonable to treat patients with hypertension to a BP goal <130/80 mmHg and with a CCB on the basis of improved glomerular filtration rate (GFR) and kidney survival. Cerebrovascular Disease • In adults with intracerebral hemorrhage (ICH) who present with SBP >220 mmHg, it is reasonable to use continuous intravenous (IV) drug infusion and close BP monitoring to lower levels. Immediate lowering of SBP to <140 mmHg in adults with spontaneous ICH who present within six hours of the acute event and have an SBP between 150 mmHg and 220 mmHg is not of benefit to reduce death or severe disability and can be potentially harmful. • Adults with acute ischemic stroke and elevated BP who are eligible for treatment

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	with IV tissue plasminogen activator (tPA) should have their BP slowly lowered to <185/110 mmHg before thrombolytic therapy is initiated. • In adults with an acute ischemic stroke, BP should be <185/110 mmHg before administration of IV tPA and should be maintained below 180/105 mmHg for at least the first 24 hours after initiation drug therapy. • Starting or restarting antihypertensive therapy during hospitalization in patients with BP >140/90 mmHg who are neurologically stable is safe and reasonable to improve long-term BP control, unless contraindicated. • In patient with BP ≥220/120 mmHg who did not receive IV alteplase or endovascular treatment and have no comorbid conditions requiring acute antihypertensive treatment, the benefit of initiating or reinitiating treatment of hypertension within the first 48 to 72 hours is uncertain. It might be reasonable to lower BP by 15% during the first 24 hours after onset of stroke. In patients with BP <220/120 mmHg with the same conditions, initiating or reinitiating treatment of hypertension within the first 48 to 72 hours after an acute ischemic stroke is not effective to prevent death or dependency. • Adults with previously treated stroke or transient ischemic attack should be restarted on antihypertensive treatment after the first few days of the index event to reduce the risk of recurrent stroke and other vascular events. Treatment with a thiazide diuretic, ACE inhibitor, or ARB, or combination treatment consisting of a thiazide diuretic plus ACE inhibitor, is useful. • Adults not previously treated for hypertension who experienced a stroke or transient ischemic attack and have an established BP ≥140/90 mmHg should be prescribed antihypertensive treatment a few days after the index event to reduce the risk of recurrent stroke and other vascular event. • For adults who experience a stroke or transient ischemic attack, selection of specific drugs should be individualized on the basis of patient comorbidities and agent pharmacological class. • For adults who experience a stroke or transient ischemic attack, a BP goal <130/80 mmHg may be reasonable. • For adults with a lacunar stroke, a target SBP goal <130 mmHg may be reasonable. • In adults previously untreated for hypertension who experience an ischemic stroke or transient ischemic attack and have an SBP <140 mmHg and a DBP <90 mmHg, the usefulness of initiating antihypertensive treatment is not well established. <u>Peripheral Artery Disease (PAD)</u> • Adults with hypertension and PAD should be treated similarly to patients with hypertension without PAD. <u>Diabetes Mellitus (DM)</u> • In adults with DM and hypertension, antihypertensive drug treatment should be initiated at a BP of ≥130/80 mmHg with a treatment goal <130/80 mmHg. • In adults with DM and hypertension, all first-line classes of antihypertensive agents (i.e., diuretics, ACE inhibitors, ARBs, and CCBs) are useful and effective. • In adults with DM and hypertension, ACE inhibitors or ARBs may be considered in the presence of albuminuria. <u>Atrial Fibrillation, Valvular Heart Disease, and Aortic disease</u> • Treatment of hypertension can be useful for prevention of recurrence of AF. • In adults with asymptomatic aortic stenosis, hypertension should be treated with pharmacotherapy, starting at a low dose and gradually titrating upward as needed. • In patients with chronic aortic insufficiency, treatment of systolic hypertension with agents that do not slow the heart rate (i.e., avoid beta-blockers) is reasonable. • Beta-blockers are recommended as the preferred antihypertensive agents in

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	patients with hypertension and thoracic aortic disease. Racial and Ethnic Differences in Treatment • In black adults with hypertension but without HF or CKD, including those with DM, initial antihypertensive treatment should include a thiazide-type diuretic or CCB. Two or more antihypertensive medications are recommended to achieve a BP target <130/80 mmHg in most adults with hypertension, especially in black adults with hypertension. Pregnancy • Women with hypertension who become pregnant, or are planning to become pregnant, should be transitioned to methyldopa, nifedipine, and/or labetalol during pregnancy. • Women with hypertension who become pregnant should not be treated with ACE inhibitors, ARBs, or direct renin inhibitors. Older Persons • Treatment of hypertension with an SBP treatment goal <130 mmHg is recommended for noninstitutionalized ambulatory community-dwelling adults (≥65 years of age) with an average SBP of ≥130 mmHg. • For older adults (≥65 years of age) with hypertension and a higher burden of comorbidity and limited life expectancy, clinical judgment, patient preference, and a team-based approach to assess risk/benefit is reasonable for decisions regarding intensity of BP lowering and choice of antihypertensive drugs. Hypertensive Crises • In adults with a hypertensive emergency, admission to an intensive care unit is recommended for continuous monitoring of BP and target organ damage and for parenteral administration of an appropriate agent. • For adults with a compelling condition (i.e., aortic dissection, severe pre-eclampsia or eclampsia, or pheochromocytoma crisis), SBP should be reduced to <140 mmHg during the first hour and to <120 mmHg in aortic dissection. • For adults without a compelling condition, SBP should be reduced by no more than 25% within the first hours; then, if stable, to 160/100 mmHg within the next two to six hours; and then cautiously to normal during the following 24 to 48 hours. Cognitive Decline and Dementia • In adults with hypertension, BP lowering is reasonable to prevent cognitive decline and dementia. Patients Undergoing Surgical Procedures • In patients with hypertension undergoing major surgery who have been on beta-blockers chronically, beta-blockers should be continued. • In patients with hypertension undergoing planned elective major surgery, it is reasonable to continue medical therapy for hypertension until surgery. • In patients with hypertension undergoing major surgery, discontinuation of ACE inhibitors or ARBs perioperatively may be considered. • In patients with planned elective major surgery and SBP ≥180 mmHg or DBP ≥110 mmHg, deferring surgery may be considered. • For patients undergoing surgery, abrupt pre-operative discontinuation of beta-blockers or clonidine is potentially harmful. • Beta-blockers should not be started on the day of surgery in beta-blocker-naïve patients. • Patients with intraoperative hypertension should be managed with IV medications

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	until such time as oral medications can be resumed.
American Diabetes Association: **Standards of Medical Care in Diabetes (2023)**[29]	Hypertension/blood pressure control • Blood pressure should be measured at every routine visit. When possible, patients found to have elevated blood pressure (systolic blood pressure 120 to 129 mmHg and diastolic <80 mmHg) should have blood pressure confirmed using multiple readings, including measurements on a separate day, to diagnose hypertension. Patients with blood pressure ≥180/110 and cardiovascular disease could be diagnosed with hypertension at a single visit. • All hypertensive patients with diabetes should monitor their blood pressure at home. • For patients with diabetes and hypertension, blood pressure targets should be individualized through a shared decision-making process that addresses cardiovascular risk, potential adverse effects of antihypertensive medications, and patient preferences. • Individuals with diabetes and hypertension qualify for antihypertensive drug therapy when the blood pressure is persistently elevated ≥130/80 mmHg. The on-treatment target blood pressure goal is <130/80 mmHg, if it can be safely attained. • In pregnant patients with diabetes and preexisting hypertension, a blood pressure target of 110 to 135/85 is suggested in the interest of reducing the risk for accelerated maternal hypertension and minimizing impaired fetal growth. • For patients with blood pressure >120/80, lifestyle intervention consists of weight loss when indicated, a Dietary Approaches to Stop Hypertension (DASH)-style eating pattern including reducing sodium and increasing potassium intake, moderation of alcohol intake, and increased physical activity. • Patients with confirmed office-based blood pressure ≥130/80 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of pharmacologic therapy to achieve blood pressure goals. • Patients with confirmed office-based blood pressure ≥160/100 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of two drugs or a single pill combination of drugs demonstrated to reduce cardiovascular events in patients with diabetes. • Treatment for hypertension should include drug classes demonstrated to reduce cardiovascular events in patients with diabetes (ACE inhibitors, angiotensin receptor blockers, thiazide-like diuretics, or dihydropyridine calcium channel blockers). ACE inhibitors or angiotensin receptor blockers are recommended first-line therapy for hypertension in people with diabetes and coronary artery disease. • Multiple-drug therapy is generally required to achieve blood pressure targets (but not a combination of ACE inhibitors and angiotensin receptor blockers). • An ACE inhibitor or angiotensin receptor blocker, at the maximum tolerated dose indicated for blood pressure treatment, is the recommended first-line treatment for hypertension in patients with diabetes and urinary albumin–to–creatinine ratio ≥300 mg/g creatinine or 30 to 299 mg/g creatinine. If one class is not tolerated, the other should be substituted. • For patients treated with an ACE inhibitor, angiotensin receptor blocker, or diuretic, serum creatinine/estimated glomerular filtration rate and serum potassium levels should be monitored at least annually. • Patients with hypertension who are not meeting blood pressure targets on three classes of antihypertensive medications (including a diuretic) should be considered for mineralocorticoid receptor antagonist therapy. Chronic kidney disease • At least once a year, assess urinary albumin (e.g., spot urinary albumin–to–creatinine ratio) and estimated glomerular filtration rate in patients with type 1 diabetes with duration of five or more years and in all patients with type 2 diabetes.

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	• In people with established diabetic kidney disease, urinary albumin (e.g., spot urinary albumin-to-creatinine ratio) and estimated glomerular filtration rate should be monitored one to four times per year depending on the stage of the disease. Optimize glucose control to reduce the risk or slow the progression of chronic kidney disease (CKD). • For patients with type 2 diabetes and diabetic kidney disease, use of a sodium-glucose cotransporter 2 inhibitor in patients with an estimated glomerular filtration rate ≥20 mL/min/1.73 m^2 and urinary albumin ≥200 mg/g creatinine is recommended to reduce CKD progression and cardiovascular events. • For patients with type 2 diabetes and diabetic kidney disease, use of a sodium–glucose cotransporter 2 inhibitor is recommended to reduce chronic kidney disease progression and cardiovascular events in patients with an estimated glomerular filtration rate ≥20 mL/min/1.73 m^2 and urinary albumin ranging from normal to 200 mg/g creatinine. • In people with type 2 diabetes and diabetic kidney disease, consider use of sodium–glucose cotransporter 2 inhibitors (if estimated glomerular filtration rate is ≥20 mL/min/1.73 m^2), a glucagon-like peptide 1 agonist, or a nonsteroidal mineralocorticoid receptor antagonist (if estimated glomerular filtration rate is ≥25 mL/min/1.73 m^2) additionally for cardiovascular risk reduction. • In people with chronic kidney disease and albuminuria who are at increased risk for cardiovascular events or chronic kidney disease progression, a nonsteroidal mineralocorticoid receptor antagonist shown to be effective in clinical trials is recommended to reduce chronic kidney disease progression and cardiovascular events. • Optimize blood pressure control and reduce blood pressure variability to reduce the risk or slow the progression of CKD. • Do not discontinue renin-angiotensin system blockade for minor increases in serum creatinine (≤30%) in the absence of volume depletion. • For people with nondialysis-dependent stage 3 or higher CKD, dietary protein intake should be a maximum of 0.8 g/kg body weight per day (the recommended daily allowance). For patients on dialysis, higher levels of dietary protein intake should be considered, since protein energy wasting is a major problem in some dialysis patients. • In nonpregnant patients with diabetes and hypertension, either an ACE inhibitor or an angiotensin receptor blocker is recommended for those with modestly elevated urinary albumin–to–creatinine ratio (30 to 299 mg/g creatinine) and is strongly recommended for those with urinary albumin–to–creatinine ratio ≥300 mg/g creatinine and/or estimated glomerular filtration rate <60 mL/min/1.73 m^2. • Periodically monitor serum creatinine and potassium levels for the development of increased creatinine and hyperkalemia when ACE inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists are used, or hypokalemia when diuretics are used. • An ACE inhibitor or an angiotensin receptor blocker is not recommended for the primary prevention of CKD in patients with diabetes who have normal blood pressure, normal urinary albumin–to–creatinine ratio (<30 mg/g creatinine), and normal estimated glomerular filtration rate. • Patients should be referred for evaluation by a nephrologist if they have continuously increasing urinary albumin levels and/or continuously decreasing estimated glomerular filtration rate and an estimated glomerular filtration rate <30 mL/min/1.73 m^2. • Promptly refer to a nephrologist for uncertainty about the etiology of kidney disease, difficult management issues, and rapidly progressing kidney disease.
American Academy of Neurology/ American Headache	• The following medications are established as effective and should be offered for migraine prevention: ○ Antiepileptic drugs: divalproex sodium, sodium valproate, topiramate.

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Society: **Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults (2012)**[30] (Reaffirmed October 2022)	○ β-blockers: metoprolol, propranolol, timolol ○ Triptans: frovatriptan for short-term menstrually associated migraine prevention. • The following medications are probably effective and should be considered for migraine prevention: ○ Antidepressants: amitriptyline, venlafaxine. ○ β-blockers: atenolol, nadolol. ○ Triptans: naratriptan, zolmitriptan for short-term menstrually associated migraine prevention. • The following medications are possibly effective and may be considered for migraine prevention: ○ Angiotensin converting enzyme inhibitors: lisinopril. ○ Angiotensin receptor blockers: candesartan. ○ α 1 agonists: clonidine, guanfacine. ○ Antiepileptic drugs: carbamazepine. ○ β-blockers: nebivolol, pindolol. • Evidence is conflicting or inadequate to support or refute the use of the following medications for migraine prevention: ○ Antiepileptic drugs: gabapentin. ○ Antidepressants: ▪ Selective serotonin reuptake inhibitor/selective/serotonin-norepinephrine reuptake inhibitors: fluoxetine, fluvoxamine. ▪ Tricyclics: protriptyline. ○ Antithrombotics: acenocoumarol, Coumadin, picotamide. ○ β-blockers: bisoprolol. ○ Calcium-channel blockers: nicardipine, nifedipine, nimodipine, verapamil. ○ Acetazolamide. ○ Cyclandelate. • The following medication is established as ineffective and should not be offered for migraine prevention: ○ Lamotrigine. • The following medication is probably ineffective and should not be considered for migraine prevention: ○ Clomipramine. • The following medications are possibly ineffective and may not be considered for migraine prevention: ○ Acebutolol. ○ Clonazepam. ○ Nabumetone. ○ Oxcarbazepine. ○ Telmisartan.
American Academy of Neurology and the American Headache Society: **Pharmacological Treatment for Pediatric Migraine Prevention (2019)** and **Acute Treatment of Migraine in Children and Adolescents**	<u>Pediatric migraine prevention</u> • Clinicians should inform patients and caregivers that in clinical trials of preventive treatments for pediatric migraine, many children and adolescents who received placebo improved and most preventive medications were not superior to placebo. • Clinicians should engage in shared decision-making regarding the use of short-term treatment trials (a minimum of two months) for those who could benefit from preventive treatment. • Clinicians should discuss the evidence for amitriptyline combined with cognitive behavioral treatment (CBT) for migraine prevention, inform patients of the potential side effects of amitriptyline including risk of suicide, and work with families to identify providers who can offer this type of treatment. • Clinicians should discuss the evidence for topiramate and propranolol for migraine prevention in children and adolescents and their side effects in this

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(2018)[31,32] (Reaffirmed October 2022)	population. • There is insufficient evidence to evaluate the effects of flunarizine, nimodipine, valproate, and onabotulinumtoxinA for use in migraine prevention in children and adolescents. • Clinicians must consider the teratogenic effects of topiramate and valproate in their choice of migraine prevention therapy recommendations to patients of childbearing potential. • Clinicians must recommend daily folic acid supplementation to patients of childbearing potential who take topiramate or valproate. <u>Pediatric migraine treatment</u> • Clinicians should prescribe ibuprofen oral solution (10 mg/kg) as an initial treatment option to reduce pain in children and adolescents with migraine. • For adolescents with migraine, clinicians should prescribe sumatriptan/naproxen tablet, zolmitriptan nasal spray (NS), sumatriptan NS, rizatriptan orally disintegrating tablet, or almotriptan tablet to reduce headache pain. • Clinicians should counsel patients and families that a series of medications may need to be used to find treatments that most benefit the patient. • Clinicians should offer an alternate triptan, if one triptan fails to provide pain relief, to find the most effective agent to reduce migraine symptoms. • Clinicians may prescribe a nonoral route when headache peaks in severity quickly, is accompanied by nausea or vomiting, or oral formulations fail to provide relief. • Clinicians should counsel patients and families that if their headache is successfully treated by their acute migraine medication, but headache recurs within 24 hours of their initial treatment, taking a second dose of acute migraine medication can treat the recurrent headache. • In adolescents whose migraine is incompletely responsive to a triptan, clinicians should offer ibuprofen or naproxen in addition to a triptan to improve migraine relief. • Clinicians must not prescribe triptans to those with a history of ischemic vascular disease or accessory conduction pathway disorders to avoid the morbidity and mortality associated with aggravating these conditions. • Clinicians may consider referral of children and adolescents with hemiplegic migraine or migraine with brainstem aura who do not respond to other treatments to a headache specialist to find effective treatment.
American Academy of Family Physicians: **Migraine Headache Prophylaxis (2019)** and **Acute Migraine Headache: Treatment Strategies (2019)**[33,34]	<u>Migraine headache prophylaxis</u> • First-line agents for prophylactic treatment include: divalproex, metoprolol, propranolol, timolol, and topiramate. • Second-line agent for prophylactic treatment include: amitriptyline, atenolol, nadolol, and venlafaxine. • Frovatriptan is a first-line treatment for the prevention of menstrual-associated migraines. Naratriptan and zolmitriptan are second-line treatments for the same indication. • Amitriptyline is considered an option for patients with depression or insomnia and is the only tricyclic antidepressant that has substantial data that supports its effectiveness. <u>Acute treatment</u> • First-line treatment options include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), triptans (e.g., almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan), and combined regimens (e.g., acetaminophen/aspirin/caffeine and sumatriptan/naproxen). ▪ Eletriptan has the least cardiovascular risk. ▪ Frovatriptan is recommended for menstrual migraine. • Second-line treatment options include antiemetics, intranasal dihydroergotamine,

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	and ketorolac. • Options for refractory migraine include intravenous dexamethasone, parenteral dihydroergotamine, intravenous magnesium sulfate, opioids, and intravenous valproate.
National Cancer Institute: **Pheochromocytoma and Paraganglioma Treatment (PDQ®) (2023)[35]**	<u>Preoperative Medical Preparation</u> • Surgery is the mainstay of treatment for most patients; however, preoperative medical preparation is critical. α-adrenergic blockade should be initiated at the time of diagnosis and maximized preoperatively to prevent potentially life-threatening cardiovascular complications, which can occur as a result of excess catecholamine secretion during surgery. Complications may include hypertensive crisis, arrhythmia, myocardial infarction, and pulmonary edema. • Phenoxybenzamine (a nonselective alpha-antagonist) is the usual drug of choice; prazosin, terazosin, and doxazosin (selective α-1-antagonists) are alternative choices. Prazosin, terazosin, and doxazosin are shorter acting than phenoxybenzamine, and therefore, the duration of postoperative hypotension is theoretically less than with phenoxybenzamine; however, there is less overall experience with selective α-1-antagonists than with phenoxybenzamine. • A preoperative treatment period of one to three weeks is usually sufficient. • Resolution of spells and a target low normal blood pressure for age indicate that α-adrenergic blockade is adequate. • During α-adrenergic blockade, liberal salt and fluid intake should be encouraged because volume loading reduces excessive orthostatic hypotension both preoperatively and postoperatively. • If tachycardia develops or if blood pressure control is not optimal with α-adrenergic blockade, a β-blocker (e.g., metoprolol or propranolol) can be added, but only after α-blockade. • A β-adrenergic blockade must never be initiated before α-blockade; doing so blocks β-blocker mediated vasodilation and results in unopposed α-blocker receptor mediated vasoconstriction, which can lead to a life-threatening crisis. <u>Localized Pheochromocytoma Treatment</u> • The standard treatment option for patients with localized pheochromocytoma is surgery. • Intraoperative hypertension can be controlled with intravenous infusion of phentolamine, sodium nitroprusside, or a short-acting calcium-channel blocker (e.g., nicardipine). • Tumor removal may be followed by a sudden drop in blood pressure that may require rapid volume replacement and intravenous vasoconstrictors (e.g., norepinephrine or phenylephrine). • Postoperatively, patients should remain in a monitored environment for 24 hours. • Postoperative hypotension is managed primarily by volume expansion, and postoperative hypertension usually responds to diuretics. <u>Pheochromocytoma During Pregnancy</u> • Phenoxybenzamine use is safe in pregnancy, but beta-adrenergic blockers should be initiated only if needed because their use has been associated with intrauterine growth restriction.
American Academy of Neurology: **Practice Parameter: Therapies for Essential Tremor: Report of the Quality Standards Subcommittee of the**	• Propranolol and primidone are agents that are most commonly used to treat essential tremor (ET). • It is recommended that propranolol, long-acting propranolol, or primidone be offered to patients who want treatment for limb tremor in ET, depending on concurrent medical conditions and potential side effects. • It is recommended that either primidone or propranolol be used as initial therapy to treat limb tremor in ET. • It is recommended that atenolol and sotalol be considered for treatment of limb

Clinical Guideline	Recommendations
American Academy of Neurology (2005)[36], Evidence-based guideline update: Treatment of essential tremor (2011 update)[37] (Reaffirmed July 2022)	tremor associated with ET, and propranolol may be considered as a treatment option for head tremor in patients with ET. • Nadolol may be considered a treatment option for limb tremor associated with ET. • Pindolol is not recommended for treatment of limb tremor in ET. • Due to the lack of evidence, a recommendation regarding the use of metoprolol in the treatment of limb tremor in ET cannot be provided. • The combination of primidone and propranolol may be used to treat limb tremor when the use of a single agent does not adequately decrease tremor. • The dosages of propranolol and primidone may need to be increased after 12 months of therapy when treating limb tremor in ET. • Levetiracetam and 3,4-diaminopyridine should not be considered for treatment of limb tremor in ET. • Clinicians may choose not to consider flunarizine for treatment of limb tremor in ET. • The evidence is insufficient to make recommendations regarding the use of pregabalin, zonisamide, or clozapine
American Academy of Pediatrics: **Clinical Practice Guideline for the Management of Infantile Hemangiomas (2019)[38]**	<u>Pharmacotherapy</u> • Clinicians should use oral propranolol as the first-line agent for Infantile Hemangiomas (IHs) requiring systemic treatment (grade A, strong recommendation) • Clinicians should dose propranolol between 2 and 3 mg/kg per • day unless there are comorbidities (e.g., PHACE syndrome) or adverse effects (e.g., sleep disturbance) that necessitate a lower dose (grade A, moderate recommendation). • Clinicians should counsel that propranolol be administered with • or after feeding and that doses be held at times of diminished oral intake or vomiting to reduce the risk of hypoglycemia (grade X, strong recommendation • Clinicians should evaluate patients for and educate caregivers about potential adverse effects of propranolol, including sleep disturbances, bronchial irritation, and clinically symptomatic bradycardia and hypotension (grade X, strong recommendation) • Clinicians may prescribe oral prednisolone or prednisone to treat IHs if there are contraindications or an inadequate response to oral propranolol (grade B, moderate recommendation). • Clinicians may recommend intralesional injection of triamcinolone and/or betamethasone to treat focal, bulky IHs during proliferation or in certain critical anatomic locations (e.g., the lip) (grade B, moderate recommendation) • Clinicians may prescribe topical timolol maleate as a therapy for thin and/or superficial IHs (grade B, moderate recommendation). • Clinicians may recommend surgery and laser therapy as treatment options in managing selected IHs (grade C, moderate recommendation) • Clinicians should educate parents of infants with an IH about the condition, including the expected natural history, and its potential for causing complications or disfigurement (grade X, strong recommendation). Clinicians should educate parents of infants with an IH about the condition, including the expected natural history, and its potential for causing complications or disfigurement (grade X, strong recommendation).

*Agent not available in the United States.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the β-adrenergic blocking agents are noted in Tables 4 and 5. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 4. FDA-Approved Indications for the Beta-Adrenergic Blocking Agents[3-22]

Indications	Single Entity Agents (A-N)								
	Acebutolol	Atenolol	Betaxolol	Bisoprolol	Carvedilol	Labetalol	Metoprolol	Nadolol	Nebivolol
Angina Pectoris									
Long-term management of angina pectoris		✔*					✔†	✔	
Cardiac Arrhythmias									
Management of ventricular premature beats	✔								
Heart Failure									
Mild to severe chronic heart failure of ischemic or cardiomyopathic origin to increase survival and, also, to reduce the risk of hospitalizations					✔				
Stable, symptomatic (NYHA Class II or III) heart failure of ischemic, hypertensive, or cardiomyopathic origin to reduce the rate of mortality plus hospitalization in patients already receiving angiotensin-converting enzyme inhibitors, diuretics, and/or digoxin							✔ (succinate)		
Hypertension									
Control of blood pressure in severe hypertension						✔ (injection)			
Hypertension	✔‡	✔‡	✔‡	✔‡	✔‡	✔‡ (tablet)	✔‡	✔‡	✔‡
Myocardial Infarction									
Hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality		✔					✔ (tartrate)		
Reduce cardiovascular mortality in clinically stable patients who have survived the acute phase of a myocardial infarction and have a left ventricular ejection fraction of ≤40% (with or without symptomatic heart failure)					✔				

*Due to coronary atherosclerosis.
†Metoprolol succinate: To reduce angina attacks and to improve exercise tolerance.
‡May be used in combination with other antihypertensive agents.
NYHA=New York Heart Association

Table 5. FDA-Approved Indications for the Beta-Adrenergic Blocking Agents (continued)[3-22]

Indications	Single Entity Agents (O-Z)					Combination Products			
	Penbutolol	Pindolol	Propranolol	Sotalol	Timolol	Atenolol and Chlor-thalidone	Bisoprolol and HCTZ	Metoprolol and HCTZ	Nadolol and Bendroflu-methiazide
Angina Pectoris									
Angina pectoris			✔* (Inderal LA®,						

Indications	Single Entity Agents (O-Z)					Combination Products			
	Penbutolol	Pindolol	Propranolol	Sotalol	Timolol	Atenolol and Chlor-thalidone	Bisoprolol and HCTZ	Metoprolol and HCTZ	Nadolol and Bendroflu-methiazide
			tablet)						
Cardiac Arrhythmias									
Abolish tachyarrhythmias due to excessive catecholamine action during anesthesia when other measure fail			✔ (injection)						
Control ventricular rate in patients with atrial fibrillation and a rapid ventricular response			✔ (tablet)						
Control ventricular rate in life-threatening digitalis-induced arrhythmias			✔ (injection)						
Documented ventricular arrhythmias, such as sustained ventricular tachycardia, that in the judgement of the physician are life-threatening				✔ †					
Maintenance of normal sinus rhythm in patients with symptomatic atrial fibrillation/atrial flutter who are currently in sinus rhythm				✔ †					
Persistent premature ventricular extrasystoles that impair the well-being of the patient and do not respond to conventional measures			✔ (injection)						
Short-term treatment of supraventricular tachycardia, including Wolff-Parkinson-White syndrome and thyrotoxicosis, to decrease ventricular rate			✔ (injection)						
Hypertension									
Hypertension		✔ ‡	✔ ‡ (oral§)		‡	✔ ‖	✔	✔ ¶	✔ ‖
Mild to moderate arterial hypertension	✔ ‡								
Hypertrophic Subaortic Stenosis									
Improves NYHA functional class in symptomatic patients with hypertrophic subaortic stenosis			✔ (Inderal LA®, tablet)						
Myocardial Infarction									
Reduce cardiovascular mortality in patients who have survived the acute phase of myocardial infarction and are clinically stable			✔ (tablet)						
Reduce cardiovascular mortality and reinfarction in patients who have survived the acute phase of myocardial infarction and are clinically stable					✔				
Other									
Adjunct to α-adrenergic blockade to control blood pressure and reduce symptoms of catecholamine-secreting tumors			✔ (tablet)						

Indications	Single Entity Agents (O-Z)					Combination Products			
	Penbutolol	Pindolol	Propranolol	Sotalol	Timolol	Atenolol and Chlor-thalidone	Bisoprolol and HCTZ	Metoprolol and HCTZ	Nadolol and Bendroflu-methiazide
Familial or hereditary essential tremor			✔ (tablet)						
Treatment of proliferating infantile hemangioma requiring systemic therapy			✔ (Hemangeol®)						
Prophylaxis of migraine headache			✔ (Inderal LA®, tablet)		✔				

*Angina pectoris due to coronary atherosclerosis to decrease angina frequency and increase exercise tolerance.
†Intravenous sotalol can substitute for oral sotalol in patients who are unable to take sotalol orally.
‡May be used in combination with other antihypertensive agents.
§Inderal LA® and propranolol tablet are not indicated in the management of hypertensive emergencies.
‖Not indicated for initial treatment of hypertension.
¶Dutoprol® and Lopressor HCT® may be used in combination with other antihypertensive agents. Lopressor HCT® is not indicated for initial treatment of hypertension.
HCTZ=hydrochlorothiazide, NYHA=New York Heart Association

IV. Pharmacokinetics

The pharmacokinetic parameters of the β-adrenergic blocking agents are listed in Table 6. The lipophilic properties vary among the agents. The higher the lipid solubility, the higher the potential to cross the blood brain barrier and increase the risk of central nervous system adverse events, including dizziness and drowsiness.[13,15]

Table 6. Pharmacokinetic Parameters of the Beta-Adrenergic Blocking Agents[2]

Generic Name(s)	Bio-availability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)	Lipid Solubility
Single Entity Agents						
Acebutolol	40	10 to 26	Liver (% not reported)	Renal (30 to 40) Bile (3 to 8) Feces (56)	3 to 4	Low
Atenolol	46 to 60	6 to 16	Not reported	Renal (40 to 50) Feces (50)	6 to 7	Low
Betaxolol	78 to 90	50 to 60	Liver, extensive (% not reported)	Renal (>80)	14 to 22	Low
Bisoprolol	80 to 94	30 to 36	Liver (50)	Renal (50) Feces (<2)	9 to 12	Low
Carvedilol	21 to 35	95 to 98	Liver, extensive (% not reported)	Renal (16) Feces (60)	7 to 10	Moderate
Labetalol	25	50	Liver, extensive (% not reported)	Renal (55 to 60) Feces (50)	5 to 8	Moderate
Metoprolol	50 to 77	12	Liver, extensive (% not reported)	Renal (95)	3 to 7	Moderate
Nadolol	20 to 40	28 to 30	None	Renal (25) Feces (77)	20 to 24	Low
Nebivolol	12 to 96	98	Liver, extensive (% not reported)	Renal (<1) Feces (13 to 44)	12 to 19	High
Penbutolol	100	80 to 98	Liver, extensive (% not reported)	Renal (90)	5	High
Pindolol	95	40 to 60	Liver (60 to 65)	Renal (35 to 40) Feces (6 to 9)	3 to 4	Moderate
Propranolol	30 to 70	93	Liver (50 to 70)	Renal (<1)	3 to 6	High
Sotalol	90 to 100	0	Liver, minor	Renal (66 to 88)	7 to 12	Low
Timolol	61	<10	Liver (80)	Renal (20)	2 to 4	Low-Moderate
Combination Products						
Atenolol and chlorthalidone	50/65	16/75	Not reported/ Liver (% not reported)	Renal (40 to 50) Feces (50)/ Renal (60)	6 to 7/ 40 to 60	Low/not reported
Bisoprolol and HCTZ	80/ 50 to 75	30/ 40 to 68	Liver (50)/ not reported	Renal (50) Feces (<2)/ Renal (>95)	9 to 12/ 6 to 15	Low/not reported
Metoprolol and HCTZ	Not reported	12/68	Liver, extensive (% not reported)/ not reported	Renal (95)/ Renal (72 to 97)	3 to 7/ 10 to 17	Moderate/ not reported
Nadolol and bendro-flumethiazide	30	Not reported	Not Reported	Not reported	20 to 24/ 3	Not reported

HCTZ=hydrochlorothiazide

V. Drug Interactions

Major drug interactions with the beta-adrenergic blocking agents (β-blockers) are listed in Table 7.

Table 7. Major Drug Interactions with the Beta-Adrenergic Blocking Agents[2]

Generic Name(s)	Interaction	Mechanism
β-blockers (acebutolol, atenolol, betaxolol, bisoprolol, carvedilol, metoprolol, nadolol, nebivolol, penbutolol, pindolol, propranolol, sotalol, timolol)	Verapamil	May be synergistic or additive effects. Verapamil may inhibit oxidative metabolism of certain β-blockers. Additive QT interval prolongation is possible with sotalol.
β-blockers (nadolol, penbutolol, pindolol, propranolol, sotalol, timolol)	Epinephrine	Nonselective β blockade allows α -receptor effects of epinephrine to predominate. Increasing vascular resistance leads to a rise in blood pressure and reflex bradycardia.
β-blockers (nadolol, penbutolol, pindolol, propranolol, sotalol, timolol)	Sympathomimetics	Nonselective β-blockers may block the action of beta-agonists, potentially resulting in severe bronchospasm in asthmatics.
Thiazides (hydrochlorothiazide, chlorthalidone, bendroflumethiazide)	Lithium	Decreased lithium clearance may occur with thiazide use. This may lead to increased serum lithium levels and possibly lithium toxicity. Monitor plasma lithium levels and symptoms of toxicity, and adjust the dose as needed.
Thiazides (hydrochlorothiazide, bendroflumethiazide)	Dofetilide	Thiazide diuretics may induce hypokalemia which may increase the risk of torsades de pointes. The coadministration of dofetilide with a thiazide diuretic is contraindicated.
β-blockers (sotalol)	Bepridil	Arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility.
β-blockers (sotalol)	Chloroquine	Prolonged QT interval and cardiac arrhythmias are a potential when sotalol and chloroquine are coadministered.
β-blockers (sotalol)	Class IA, IC, III Antiarrhythmic Agents	Class IA, IC, and III antiarrhythmics and sotalol may cause additive pharmacologic and adverse cardiovascular effects when co- administered.
β-blockers (sotalol)	Dofetilide	The risk of cardiovascular toxicity, including torsades de pointes, may be increased by co-administration of dofetilide and sotalol. Pharmacologic effects of dofetilide and sotalol on electrical conduction of the heart may be additive.
β-blockers (sotalol)	Dronedarone	Arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility.
β-blockers (sotalol)	Droperidol	Arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility.
β-blockers (sotalol)	Fluconazole	Coadministration of fluconazole and sotalol may increase the risk of potentially fatal cardiac arrhythmias (torsades de pointes), especially in seriously ill patients and/or patients receiving high dose fluconazole.
β-blockers (sotalol)	Haloperidol	Arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility.

Generic Name(s)	Interaction	Mechanism
β-blockers (sotalol)	Maprotiline	Arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility.
β-blockers (sotalol)	Methadone	Prolongation of the QT interval with possible development of cardiac arrhythmias, including torsades de pointes, should be considered when sotalol is co-administered with methadone.
β-blockers (sotalol)	Nilotinib	Additive QT prolongation may occur during coadministration of nilotinib and sotalol.
β-blockers (sotalol)	Pentamidine	Prolongation of the QT interval with possible development of cardiac arrhythmias, including torsades de pointes, should be considered when sotalol is co-administered with pentamidine.
β-blockers (sotalol)	Perflutren	Additive QT interval prolongation may occur during coadministration of perflutren and sotalol.
β-blockers (sotalol)	Phenothiazines	Arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility when sotalol and phenothiazines are co-administered.
β-blockers (sotalol)	Phosphodiesterase type 5 Inhibitors	Phosphodiesterase type 5 inhibitors and sotalol may cause additive adverse effects when co-administered. Prolonged QT interval with the potential for cardiac arrhythmias may occur.
β-blockers (sotalol)	Pimozide	Sotalol and pimozide may cause additive adverse effects when co-administered. Cardiovascular toxicity, including torsades de pointes, may occur due to additive QT-interval prolongation.
β-blockers (sotalol)	Quinolones	The rare occurrence of arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility.
β-blockers (sotalol)	Serotonin Receptor Antagonists Antiemetics	The risk of QT-interval prolongation and cardiac arrhythmias caused by serotonin receptor antagonist antiemetics may be increased by co-administration of sotalol.
β-blockers (sotalol)	Tetrabenazine	Additive QT prolongation may occur during coadministration of tetrabenazine and sotalol.
β-blockers (sotalol)	Tyrosine Kinase Receptor Inhibitor	Additive QT interval prolongation is a possibility when tyrosine kinase receptor inhibitors are coadministered with sotalol.
β-blockers (sotalol)	Ziprasidone	Arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility when sotalol and ziprasidone are co-administered.
β-blockers (acebutolol, atenolol, betaxolol, bisoprolol, metoprolol, nadolol, nebivolol, penbutolol, pindolol, propranolol, sotalol, timolol)	Clonidine	B-blocker inhibition of β_2 receptor mediated vasodilation leaves peripheral α_2-receptor mediated vasoconstriction unopposed to clonidine stimulation.
β-blockers (acebutolol, atenolol, betaxolol, carvedilol, metoprolol, nadolol, nebivolol, penbutolol, pindolol, propranolol, sotalol, timolol)	Diltiazem	Additive AV nodal blockade may lead to synergistic bradycardia
β-blockers (acebutolol, atenolol, betaxolol, bisoprolol, carvedilol,	Flecainide	Unknown mechanism. Combination may result in additive bradycardia and cardiac arrest

Generic Name(s)	Interaction	Mechanism
metoprolol, nadolol, nebivolol, penbutolol, pindolol, propranolol, timolol)		
β-blockers (acebutolol, atenolol, betaxolol, carvedilol, metoprolol, nadolol, nebivolol, penbutolol, pindolol, propranolol, sotalol, timolol)	Nonsteroidal Anti-inflammatory Drugs	NSAIDs may inhibit renal prostaglandin synthesis, allowing unopposed pressor systems to produce hypertension.
β-blockers (acebutolol, atenolol, betaxolol, carvedilol, metoprolol, nadolol, nebivolol, penbutolol, pindolol, propranolol, sotalol, timolol)	Quinazolines	Unknown mechanism. Additive vasodilation may increase risk of hypotension, specifically orthostatic hypotension. Generally occurs with the addition of prazosin to chronic β-blocker therapy, not β-blocker added to chronic prazosin therapy
β-blockers (bisoprolol, carvedilol, nadolol, penbutolol, pindolol, propranolol, sotalol, timolol)	Insulin	β-blockers blunt sympathetic mediated responses to hypoglycemia.
β-blockers (atenolol, carvedilol, metoprolol, nadolol, pindolol, propranolol, sotalol)	Lidocaine	Reduced hepatic lidocaine metabolism and possibly a minor component of diminished hepatic blood flow.
β-blockers (bisoprolol, carvedilol, metoprolol, pindolol, propranolol, timolol)	Cimetidine	Cimetidine may reduce hepatic first-pass extraction, decrease liver blood flow, and inhibit hepatic metabolism of β-blockers.
β-blockers (nadolol, penbutolol, pindolol, propranolol, sotalol, timolol)	Meglitinides	Unknown mechanism. Possible increase in hypoglycemic activity of meglitinides.
β-blockers (nadolol, penbutolol, pindolol, propranolol, sotalol, timolol)	Theophyllines	Pharmacologic antagonism. B-blockers may reduce the n-demethylation of theophylline.
β-blockers (atenolol, carvedilol, metoprolol, propranolol, timolol)	Quinidine	Oxidative metabolism of certain β-blockers may be inhibited by quinidine.
β-blockers (carvedilol, metoprolol, nebivolol, propranolol, timolol)	Terbinafine	Terbinafine inhibits CYP2D6 and may result in increased plasma concentrations of certain β-blockers.
β-blockers (carvedilol, metoprolol, propranolol, timolol)	Diphenhydramine	Inhibition of CYP2D6-mediated β-blocker metabolism may decrease the metabolism of certain β-blockers resulting in excessive cardiovascular effects.
β-blockers (metoprolol, nebivolol, propranolol, timolol)	Serotonin Reuptake Inhibitors	Inhibition of CYP2D6 enzyme may decrease the metabolism of metoprolol resulting in excessive pharmacologic activity.
β-blockers (metoprolol, propranolol, sotalol)	Amiodarone	Additive pharmacologic effects of both drugs may result in severe bradycardia, hypotension, or cardiac arrest. Possible additive QT interval prolongation with sotalol and amiodarone.
β-blockers (pindolol, propranolol, sotalol)	Phenothiazines	Chlorpromazine may inhibit the first-pass hepatic metabolism of propranolol and increase its pharmacologic effects. Certain β-blockers may inhibit the metabolism of phenothiazines increasing the risk for cardiac side effects, including torsades

Generic Name(s)	Interaction	Mechanism
		de pointes.
β-blockers (carvedilol, metoprolol, propranolol)	Rifamycins (rifabutin, rifampin, rifapentine)	Possible decrease in oral bioavailability of carvedilol resulting in first-pass metabolism.
β-blockers (carvedilol, metoprolol, propranolol)	Thiamines	Hyperthyroidism appears to cause increased clearance of β-blockers with a high extraction ration. This may be the result of increased liver blood flow, first-pass metabolism and volume of distribution.
Thiazide diuretics (HCTZ, chlorthalidone, bendroflumethiazide)	Diazoxide	The combination of diazoxide with a thiazide diuretic may lead to hyperglycemia though an unknown mechanism; therefore the combination should be avoided. When used together, blood and urine glucose levels should be frequently monitored, and dosage reductions may be required.
Thiazide diuretics (HCTZ, chlorthalidone, bendroflumethiazide)	Digitalis glycosides	Thiazide diuretics may induce electrolyte disturbances which may predispose patients to digitalis-induced arrhythmias. Measure plasma levels of potassium and magnesium, supplement low levels, and use dietary sodium restriction or potassium-sparing diuretics to prevent further losses.
β-blockers (metoprolol, propranolol)	Hydralazine	Hydralazine increases systemic availability of some β-blockers, probably by transient increase in splanchnic blood flow and decreasing first-pass hepatic metabolism.
β-blockers (metoprolol, propranolol)	Propafenone	Propafenone increases plasma β-blocker level by decreasing first-pass metabolism and reducing systemic clearance. Both drugs are oxidized by the hepatic CYP450 system, and propafenone appears to inhibit the metabolism of the β-blocker.
β-blockers (atenolol)	Ampicillin	The bioavailability of atenolol may be decreased by impaired gastrointestinal absorption induced by ampicillin.
β-blockers (carvedilol)	Cyclosporine	Unknown mechanism. Carvedilol may increase plasma concentrations of cyclosporine and dose reduction may be required.
β-blockers (carvedilol)	Digoxin	Carvedilol may increase digoxin bioavailability. Possible additive depression of myocardial conduction and decreased renal tubular digoxin secretion.
β-blockers (labetalol)	Inhalation anesthetics	Additive myocardial depressant effects possibly resulting in excessive hypotension.
β-blockers (propranolol)	Mefloquine	Additive slowing of cardiac conduction possibly resulting in lengthening of the QT interval
β-blockers (propranolol)	Triptans	Unknown mechanism. Possible inhibition of triptan metabolism (monoamine oxidase-A) by propranolol resulting in enhanced pharmacologic effects and plasma concentrations.
β-blockers (sotalol)	Cisapride	Prolongation of the QT interval with possible development of cardiac arrhythmias, including torsades de pointes, should be considered when cisapride is co-administered with sotalol.
β-blockers (sotalol)	H1 Antagonists	The rare occurrence of arrhythmias resulting from the potential for additive QT prolongation should

Generic Name(s)	Interaction	Mechanism
		be considered as a possibility when sotalol and H-1 antagonists are coadministered.
β-blockers (sotalol)	Iloperidone	Prolonged QT interval and cardiac arrhythmias are a potential when sotalol and iloperidone are used concomitantly.
β-blockers (sotalol)	Macrolides	The rare occurrence of arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility when sotalol and macrolides are coadministered.
β-blockers (sotalol)	Mefloquine	Co-administration of mefloquine and sotalol may cause cardiovascular toxicity, including electrocardiographic abnormalities such as QT interval prolongation
β-blockers (sotalol)	Mibefradil	Co-administration of sotalol and mibefradil may cause cardiovascular toxicity.
β-blockers (sotalol)	Paliperidone	Prolongation of the QT interval with possible development of cardiac arrhythmias, including torsades de pointes, should be considered when paliperidone is co-administered with sotalol.
β-blockers (sotalol)	Propafenone	The rare occurrence of arrhythmias resulting from the potential for additive QT prolongation should be considered when sotalol and propafenone are coadministered.
β-blockers (sotalol)	Saquinavir	Coadministration of sotalol with saquinavir/ritonavir may be associated arrhythmias due to potential additive effects on prolongation of the QT interval.
β-blockers (sotalol)	Tricyclic Antidepressants	The rare occurrence of arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility when tricyclic antidepressants and sotalol are coadministered.
β-blockers (acebutolol)	Ceritinib	Bradycardia causing agents may enhance the bradycardic effect of ceritinib.
β-blockers (acebutolol, atenolol, betaxolol, bisoprolol, carvedilol, labetalol, metoprolol, nadolol, nebivolol, pindolol, propranolol, timolol)	Rivastigmine	Concurrent use may result in additive bradycardic effects.
β-blockers (carvedilol, labetalol, nadolol, pindolol, propranolol, timolol)	Beta2-agonists (non-selective)	Nonselective beta-blockers may diminish the bronchodilatory effect of beta2-agonists
β-blockers (carvedilol)	Topotecan	P-glycoprotein/ABCB1 inhibitors may increase the serum concentration of topotecan
β-blockers (carvedilol)	Vincristine	P-glycoprotein/ABCB1 inhibitors may increase the serum concentration of vincristine
β-blockers (pindolol, propranolol, sotalol)	Thioridazine	Concurrent use may result in increased risk of thioridazine toxicity (e.g., QT prolongation, torsades de pointes, cardiac arrest)
β-blockers (sotalol)	Fingolimod	Concurrent use may result in increased risk of QT interval prolongation, bradycardia, or heart block

CYP=cytochrome P450 isoenzymes, HCTZ=hydrochlorothiazide

VI. Adverse Drug Events

The most common adverse drug events reported with the β-adrenergic blocking agents are listed in Tables 8 and 9. The boxed warnings for the β-adrenergic blocking agents are listed in Tables 10 through 15.

Table 8. Adverse Drug Events (%) Reported with the Beta-Adrenergic Blocking Agents[1-3]

Adverse Events	Single Entity Agents (A-N)								
	Acebutolol	Atenolol	Betaxolol	Bisoprolol	Carvedilol	Labetalol	Metoprolol	Nadolol	Nebivolol
Cardiovascular									
Angina	-	-	<2	-	1 to 6	-	-	-	-
Arrhythmia	-	-	<2	<1	-	-	-	<1	-
Arterial/vascular insufficiency	-	-	-	-	-	-	1	-	<1
Bradycardia	1 to 10	18	6 to 8	<1	2 to 10	<1	2 to 16	1 to 10	≤1
Cardiogenic shock	-	-	-	-	-	-	✔	-	-
Cerebrovascular accident	-	-	-	-	≤4	-	-	-	-
Chest pain	2	1 to 10	2 to 7	1 to 2	-	-	1	<1	≤1
Cold extremities	-	12	2	<1	-	-	1	1 to 10	-
Congestive heart failure	1 to 10	1 to 10	<2	<1	-	<1	1	1 to 10	-
Edema	2	1 to 10	≤2	<1	5 to 6	≤2	-	1 to 10	-
Flushing	-	-	-	<1	-	1	-	-	-
Heart block	✔	1 to 10	<2	-	≤4	<1	5	-	-
Hypertension	-	-	<2	-	≤4	-	-	-	-
Hypotension	2	25	<2	<1	9 to 20	1 to 5	1 to 27	-	-
Myocardial ischemia	-	-	-	-	-	-	-	-	<1
Orthostatic hypotension	-	1 to 10	-	<1	-	-	-	<1	-
Palpitations	✔	-	2	<1	≤4	-	1	1 to 10	-
Peripheral circulation reduced	-	-	-	-	<1	-	-	1 to 10	-
Peripheral edema	-	-	-	-	1 to 7	-	1	-	1
Postural hypotension	-	-	-	-	≤4	-	-	-	-
Rhythm disturbance	-	-	-	<1	-	-	-	-	-
Shortness of breath	-	-	-	-	-	-	✔	-	-
Syncope	-	-	<2	<1	3 to 8	<1	1	-	<1
Ventricular arrhythmias	✔	-	-	-	-	-	-	-	-
Central Nervous System									
Abnormal dreams	2	1 to 10	<1	-	-	-	-	-	-
Anxiety	1 to 10	-	-	<1	-	-	✔	-	-
Concentration decreased	-	-	-	-	<1	-	-	-	-
Confusion	-	1 to 10	-	<1	-	-	✔	<1	-
Depression	2	1 to 10	<1	<1	1 to 10	-	5	1 to 10	-
Diaphoresis	-	-	<2	-	<1	-	-	-	-
Dizziness	6	1 to 10	-	<1	2 to 32	1 to 20	2 to 10	-	2 to 4
Drowsiness	-	1 to 10	-	-	-	-	-	>10	-
Fatigue	11	1 to 10	3 to 10	6 to 8	4 to 24	1 to 11	1 to 10	-	-
Fever	-	-	<2	-	1 to 10	-	-	-	-
Hallucinations	-	<1	<2	<1	-	-	✔	<1	2 to 5
Headache	6	1 to 10	-	<1	5 to 8	2	✔	<1	-

Adverse Events	Single Entity Agents (A-N)								
	Acebutolol	**Atenolol**	**Betaxolol**	**Bisoprolol**	**Carvedilol**	**Labetalol**	**Metoprolol**	**Nadolol**	**Nebivolol**
Hyper/hypoesthesia	1 to 10	-	-	1 to 2	1 to 10	-	-	-	-
Insomnia	3	1 to 10	1 to 5	2 to 3	1 to 10	-	✔	>10	6 to 9
Lethargy	-	1 to 10	3	-	-	-	-	-	1
Malaise	-	-	<2	<1	1 to 10	-	-	-	-
Memory loss	-	-	<2	<1	<1	-	✔	-	-
Mental impairment	-	1 to 10	-	-	-	-	-	-	-
Nervousness	-	-	-	<1	<1	-	✔	<1	-
Nightmares/vivid dreams	-	1 to 10	-	-	<1	-	✔	-	-
Paresthesia	-	-	-	<1	-	-	✔	-	-
Psychosis	-	<1	-	-	-	-	-	-	-
Sleep disturbance	-	-	-	<1	-	-	✔	-	-
Somnolence	-	-	-	<1	1 to 10	3	✔	-	-
Vertigo	-	-	-	<1	1 to 10	1 to 2	✔	-	<1
Dermatologic									
Acne	-	-	-	<1	-	-	-	-	-
Alopecia	-	<1	<2	<1	<1	<1	✔	-	-
Dermatitis	-	-	-	<1	-	-	-	-	✔
Eczema	-	-	-	<1	-	-	-	-	-
Erythema multiforme	-	-	-	-	<1	-	-	-	-
Exfoliative dermatitis	-	-	-	-	<1	-	-	-	-
Photosensitivity	-	-	-	-	<1	-	✔	-	-
Pruritus	1 to 10	-	-	<1	<1	1	5	-	<1
Psoriasiform rash	-	<1	-	<1	-	<1	-	-	-
Psoriasis (exacerbated)	-	-	-	<1	-	-	✔	-	<1
Purpura	-	-	-	<1	-	-	-	-	-
Rash	2	-	1	<1	<1	1	5	-	≤1
Scalp tingling	-	-	-	-	-	≤7	-	-	-
Stevens-Johnson syndrome	-	-	-	-	<1	-	-	-	-
Sweating, excessive	-	-	-	-	-	-	✔	-	-
Systemic lupus erythematosus	✔	-	-	-	-	-	-	-	-
Toxic epidermal necrolysis	-	-	-	-	<1	-	-	-	-
Urticaria	-	-	-	-	-	<1	✔	-	<1
Endocrine and Metabolic									
Diabetes (exacerbated)	-	-	<2	-	1 to 10	-	✔	-	-
Gout	-	-	-	<1	1 to 10	-	-	-	-
Libido decreased	-	-	-	-	-	-	✔	-	-
Gastrointestinal									
Abdominal pain	1 to 10	-	-	<1	1 to 10	-	✔	-	1 to 10
Anorexia	✔	-	<2	-	-	-	-	-	-
Constipation	4	1 to 10	<2	<1	-	-	1	1 to 10	-
Cramping								-	-
Diarrhea	4	1 to 10	2	3 to 4	-	-	5	1 to 10	2 to 3
Dyspepsia	4	-	4 to 5	<1	-	≤4	-	-	-
Epigastric distress	-	-	-	-	-	-	-	-	-
Flatulence	3	-	-	-	-	-	1	-	-
Gastritis/gastric irritation	-	-	-	<1	-	-	-	-	-

Adverse Events	Single Entity Agents (A-N)								
	Acebutolol	Atenolol	Betaxolol	Bisoprolol	Carvedilol	Labetalol	Metoprolol	Nadolol	Nebivolol
Gastrointestinal hemorrhage	-	-	-	-	<1	-	-	-	-
Heartburn	-	-	-	-	-	-	1	-	-
Melena	-	-	-	-	1 to 10	-	-	-	-
Nausea	4	1 to 10	2 to 6	2	2 to 9	≤19	1	1 to 10	1 to 3
Pancreatitis	-	-	-	-	<1	-	-	-	-
Peptic ulcer	-	-	-	<1	-	-	-	-	-
Periodontitis	-	-	-	-	1 to 10	-	-	-	-
Retroperitoneal fibrosis	-	-	-	-	-	-	✔	-	-
Stomach discomfort								1 to 10	-
Taste disorder	-	-	<2	<1	-	1	✔	-	-
Vomiting	1 to 10	-	<2	1 to 2	1 to 6	≤3	✔	1 to 10	<1
Weight gain	-	-	<2	<1	10 to 12	-	✔	-	-
Xerostomia	✔	-	<2	<1	<1	-	-	-	-
Genitourinary									
Cystitis	-	-	<2	<1	-	-	-	-	-
Diabetes insipidus	-	-	-	-	-	<1	-	-	-
Dysuria	1 to 10	-	<2	-	-	-	-	-	-
Ejaculatory failure	-	-	-	-	-	≤5	-	-	-
Hematuria	-	-	-	-	1 to 10	-	-	-	-
Impotence	1 to 10	1 to 10	-	<1	1 to 10	1 to 4	✔	-	<1
Libido decreased	-	-	<2	<1	<1	-	-	-	-
Micturition (frequency)	3	-	-	-	-	-	-	-	-
Nocturia	1 to 10	-	-	-	-	-	-	-	-
Polyuria	-	-	-	<1	-	-	-	-	-
Sexual ability decreased								>10	-
Urinary incontinence	-	-	-	-	<1	-	-	-	-
Urinary retention	✔	-	-	-	-	<1	-	-	-
Hematologic									
Agranulocytosis	-	-	-	-	<1	-	✔	-	-
Anemia (aplastic/hemolytic)	-	-	<2	-	1 to 10	-	-	-	-
Claudication	-	-	-	-	-	-	✔	-	-
Leukopenia	-	-	-	<1	<1	-	-	<1	-
Pancytopenia	-	-	-	-	<1	-	-	-	-
Prothrombin decreased	-	-	-	-	1 to 10	-	-	-	-
Purpura	-	-	<2	-	1 to 10	-	-	-	-
Thrombocytopenia	-	<1	<2	<1	1 to 10	-	✔	<1	1 to 10
Hepatic									
Cholestatic jaundice	-	-	-	-	<1	<1	-	-	-
Hepatic impairment	✔	-	-	-	<1	<1	-	-	-
Hepatitis	-	-	-	-	-	<1	✔	-	-
Increase liver enzymes	-	<1	-	-	-	-	-	-	<1
Transaminases increase	✔	-	<2	<1	1 to 10	4	✔	-	-
Laboratory Test Abnormalities									
Alkaline phosphatase increased	✔	-	-	-	-	-	✔	-	-
Hypercalcemia	-	-	-	-	<1	-	-	-	-
Hypercholesterolemia	-	-	<2	-	1 to 4	-	-	-	1 to 10

Adverse Events	Single Entity Agents (A-N)								
	Acebutolol	Atenolol	Betaxolol	Bisoprolol	Carvedilol	Labetalol	Metoprolol	Nadolol	Nebivolol
Hyperglycemia	-	-	<2	-	-	-	-	-	-
Hyperkalemia	-	-	<2	<1	1 to 10	-	-	-	-
Hypernatremia	-	-	-	-	-	-	-	-	-
Hyperphosphatemia	-	-	-	-	3 to 6	-	-	-	-
Hypertriglyceridemia	-	-	-	<1	1	-	-	-	-
Hyperuricemia	-	-	<2	<1	1 to 10	-	-	-	1 to 10
Hypervolemia	-	-	-	-	≤4	-	-	-	-
Hypoglycemia	-	✔	<2	<1	1 to 10	-	-	-	-
Hyponatremia	-	-	-	-	1 to 10	-	-	-	-
Hypokalemia	-	-	<2	-	1 to 10	-	-	-	-
Lactate dehydrogenase increased	-	-	-	-	-	-	✔	-	-
Musculoskeletal									
Arthralgia	-	-	3 to 5	1 to 10	1 to 6	-	✔	-	-
Arthritis	-	-	-	-	-	-	✔	-	-
Asthenia	-	-	-	≤2	-	-	-	-	-
Back pain	1 to 10	-	-	<1	2 to 7	-	-	-	-
Joint pain	1 to 10	-	-	<1	-	-	-	-	-
Muscle cramps	-	-	<2	<1	1 to 10	-	-	-	-
Muscle pain	-	-	-	<1	-	-	✔	-	-
Muscle spasm	-	-	-	-	-	-	-	-	-
Myalgia	2	-	-	-	-	-	-	-	-
Neuralgia	-	-	<2	-	<1	-	-	-	-
Paresthesia	-	-	-	-	-	≤5	-	-	1 to 10
Peripheral ischemia	✔	-	-	-	-	-	-	-	-
Restlessness	-	-	-	<1	-	-	-	-	-
Tremor	-	-	<2	<1	-	-	-	-	-
Toxic myopathy	-	-	-	-	-	<1	-	-	-
Twitching	-	-	<2	<1	-	-	-	-	-
Weakness	-	-	-	-	7 to 11	1	-	-	1 to 10
Renal									
Blood urea nitrogen increased	-	-	-	<1	≤6	≤8	-	-	1 to 10
Creatinine increase	-	-	-	<1	1 to 10	-	-	-	-
Glycosuria	-	-	-	-	1 to 10	-	-	-	-
Hematuria	-	-	-	1 to 10	-	-	-	-	-
Interstitial nephritis	-	-	-	-	<1	-	-	-	-
Renal colic	-	-	-	<1	-	-	-	-	-
Renal failure/dysfunction	-	-	-	-	1 to 10	-	-	-	<1
Respiratory									
Asthma	-	-	-	<1	<1	-	-	-	-
Bronchitis	-	-	-	<1	-	-	-	-	-
Bronchospasm	-	✔	-	<1	<1	<1	1	1 to 10	<1
Cough	1	-	<2	<1	5 to 8	-	-	-	-
Dyspnea	4	<1	2	1 to 2	>3	2	1 to 3	<1	≤1
Eosinophilic pneumonitis	-	-	-	-	<1	-	-	-	-
Interstitial pneumonitis	-	-	-	-	<1	-	-	-	-
Nasal congestion	-	-	-	-	1	1 to 6	-	-	-

Adverse Events	Single Entity Agents (A-N)								
	Acebutolol	**Atenolol**	**Betaxolol**	**Bisoprolol**	**Carvedilol**	**Labetalol**	**Metoprolol**	**Nadolol**	**Nebivolol**
Nasopharyngitis	-	-	-	-	4	-	-	-	-
Pharyngitis	1 to 10	-	2	<1	-	-	-	-	-
Pleurisy	✔	-	-	-	-	-	-	-	-
Pneumonitis	✔	-	-	-	-	-	-	-	-
Pulmonary edema	-	-	-	-	>3	-	-	-	<1
Pulmonary granulomas	✔	-	-	-	-	-	-	-	-
Respiratory failure/distress	-	-	-	-	<1	-	-	-	-
Rhinitis	2	-	-	3 to 4	2	-	✔	-	-
Sinus congestion	-	-	-	-	1	-	-	-	-
Sinusitis	-	-	-	2	-	-	-	-	-
Upper respiratory infection	-	-	-	5	-	-	-	-	-
Wheezing	1 to 10	<1	-	-	-	-	1	-	-
Special Senses									
Abnormal/blurred vision	2	-	-	-	1 to 5	1	✔	-	-
Blepharitis	-	-	<2	-	-	-	-	-	-
Cataract	-	-	<2	-	-	-	-	-	-
Conjunctivitis	1 to 10	-	-	-	-	-	-	-	-
Dry eyes	1 to 10	-	-	-	-	-	✔	-	-
Eye pain	1 to 10	-	-	<1	-	-	-	-	-
Hearing decreased	-	-	<2	<1	<1	-	-	-	-
Lacrimation, abnormal	-	-	-	<1	-	-	-	-	-
Tinnitus	-	-	<2	<1	<1	-	-	-	-
Visual disturbances	-	-	<2	<1	-	-	✔	-	-
Other									
Allergy/allergic reaction	-	-	-	-	1 to 10	-	-	-	-
Anaphylactoid reaction	-	-	-	-	<1	<1	-	-	-
Angioedema	-	-	-	-	-	<1	-	-	<1
Cholecystitis	-	-	-	-	-	-	-	-	-
Cutaneous vasculitis	-	-	-	<1	-	-	-	-	-
Diaphoresis	-	-	-	-	-	≤4	-	-	-
Gangrene	-	-	-	-	-	-	✔	-	-
Hypersensitivity	-	-	-	-	-	<1	-	-	<1
Lupus syndrome	✔	<1	-	-	-	<1	-	-	-
Metabolic acidosis	-	-	<2	-	-	-	-	-	-
Necrotizing angiitis	-	-	-	-	-	-	-	-	-
Peyronie's disease	-	<1	<2	<1	-	<1	<1	-	-
Positive antinuclear antibody test	-	<1	5	<1	1 to 10	<1	-	-	-
Tinnitus	-	-	-	-	-	-	✔	-	-

✔ Percent not specified
-Event not reported

Table 9. Adverse Drug Events (%) Reported with the Beta-Adrenergic Blocking Agents[1-3]

Adverse Events	Single Entity Agents (O-Z)					Combination Products				
	Penbutolol	Pindolol	Propranolol	Sotalol	Timolol	Atenolol and Chlor-thalidone	Bisoprolol and HCTZ	Metoprolol and HCTZ	Nadolol and Bendro-flumethiazide	
Cardiovascular										
Angina	-	-	✔	-	✔	-	-	-	-	
Arrhythmia	1 to 10	-	-	5	✔	-	<1	-	<1	
Arterial/vascular insufficiency	-	-	✔	-	-	-	-	1	-	
Atrioventricular nodal disturbances	-	-	✔	-	-	-	-	-	-	
Bradycardia	<1	≤2	6	8 to 16	1 to 10	1 to 10	<1	2 to 16	1 to 10	
Cardiac failure/arrest	-	-	-	-	1 to 10	-	-	-	-	
Cardiogenic shock	-	-	✔	-	-	-	-	✔	-	
Chest pain	-	3	2 to 4	3 to 16	-	1 to 10	1 to 2	1	<1	
Cold extremities	<1	≤2	7 to 8	<1	1 to 10	1 to 10	<1	1	1 to 10	
Congestive heart failure	1 to 10	<1	✔	5	-	1 to 10	<1	1	1 to 10	
Edema	<1	10	2	2 to 8	✔	1 to 10	<1	-	1 to 10	
Electrocardiogram abnormal	-	-	-	2 to 7	-	-	-	-	-	
Flushing	-	-	-	-	-	-	<1	-	-	
Heart block	<1	≤2	-	-	✔	1 to 10	-	5	-	
Hypotension	<1	≤2	✔	3 to 6	✔	1 to 10	1 to 10	1 to 27	-	
Myocardial contractility impaired	-	-	✔	-	-	-	<1	<1	-	
Myocardial ischemia	-	-	-	-	-	-	-	-	-	
Orthostatic hypotension	-	-	-	-	-	-	1 to 10	1 to 10	<1	
Palpitations	-	≤1	-	3 to 14	1 to 10	-	<1	1	1 to 10	
Peripheral circulation reduced	-	-	-	3	-	-	-	-	1 to 10	
Peripheral edema	-	-	-	-	-	-		1	-	
Rhythm disturbance						-	<1	-	-	
Shortness of breath						-	-	✔	-	
Syncope	-	≤2	✔	5	-	-	<1	1	-	
Tachycardia	-	≤2	-	-	-	-	-	-	-	
Torsade de pointes	-	-	-	1 to 4	-	-	-	-	-	
Thrombosis, mesenteric arterial	-	-	✔	-	-	-	-	-	-	
Central Nervous System										
Abnormal dreams	-	-	3	-	-	-	-	-	-	
Amnesia	-	-	✔	-	-	-	-	-	-	
Anxiety	-	-	-	2 to 4	✔	-	<1	✔	-	
Catatonia	-	-	✔	-	-	-	-	-	-	
Cerebral ischemia	-	-	-	-	1 to 10	-	-	-	-	
Cerebral vascular accident	-	-	-	-	1 to 10	-	-	-	-	
Cognitive dysfunction	-	-	✔	-	-	-	-	-	-	
Confusion	<1	-	✔	6	✔	1 to 10	<1	✔	<1	
Depression	1 to 10	-	1 to 3	1 to 4	✔	1 to 10	<1	5	1 to 10	
Disorientation	-	-	-	-	✔	-	-	-	✔	
Dizziness	1 to 10	9	2 to 11	3 to 20	1 to 10	1 to 10	<1	2 to 10	-	
Drowsiness	-	-	2	-	-	-	-	-	>10	

Adverse Events	Single Entity Agents (O-Z)					Combination Products				
	Penbutolol	Pindolol	Propranolol	Sotalol	Timolol	Atenolol and Chlor-thalidone	Bisoprolol and HCTZ	Metoprolol and HCTZ	Nadolol and Bendro-flumethiazide	
Emotional lability	-	-	✔	<1	-	-	-	-	-	
Fatigue	1 to 10	8	3 to 17	5 to 20	1 to 10	1 to 10	6 to 8	1 to 10	✔	
Hallucinations	-	<1	✔	-	✔	<1	<1	✔	<1	
Headache	1 to 10	-	1 to 9	2 to 12	-	1 to 10	<1	✔	<1	
Hyper/hypoesthesia	-	-	-	-	-	-	1 to 2	-	-	
Insomnia	<1	10	3 to 8	2 to 4	✔	1 to 10	2 to 3	✔	>10	
Lethargy	<1	-	4	-	-	1 to 10	-	-	-	
Lightheadedness	-	-	✔	12	-	-	-	-	-	
Malaise	-	-	-	-	-	-	<1	-	-	
Memory loss	-	-	-	-	✔	-	<1	✔	-	
Mental impairment	-	-	-	-	-	1 to 10	-	-	-	
Nervousness	-	7	2	-	✔	-	<1	✔	<1	
Nightmares/vivid dreams	<1	5	✔	-	✔	1 to 10	-	✔	✔	
Paresthesia	-	-	-	-	-	<1	<1	✔	-	
Psychosis	-	-	✔	-	-	<1	-	-	-	
Sleep disturbance	-	-	-	1 to 8	-	-	<1	✔	-	
Somnolence	-	-	✔	-	✔	-	<1	✔	✔	
Vertigo	-	-	✔	<1	-	-	<1	✔	-	
Dermatologic										
Acne	-	-	-	-	-	-	<1	-	-	
Alopecia	-	-	✔	<1	1 to 10	<1	<1	<1	-	
Cutaneous ulcers	-	-	✔	-	-	-	-	-	-	
Dermatitis	-	-	✔	-	-	-	-	-	-	
Eczematous eruptions	-	-	✔	-	-	-	-	-	-	
Erythema multiforme	-	-	✔	-	-	-	<1	<1	✔	
Exfoliative dermatitis	-	-	✔	-	-	-	<1	<1	✔	
Hyperkeratosis	-	-	✔	-	-	-	-	-	-	
Nail changes	-	-	✔	-	-	-	-	-	-	
Oculomucocutaneous reactions	-	-	✔	-	-	-	-	-	-	
Photosensitivity	-	-	-	<1	-	1 to 10	1 to 10	1 to 10	✔	
Pruritus	-	1	✔	<1	-	-	<1	5	-	
Pseudo pemphigoid	-	-	-	-	✔	-	-	-	-	
Psoriasiform rash	-	-	✔	-	✔	<1	<1	-	-	
Psoriasis (exacerbated)	-	-	-	-	1 to 10	-	<1	✔	✔	
Purpura	-	-	-	-	-	<1	<1	-	✔	
Rash	-	-	0 to 2	2 to 5	1 to 10	<1	<1	5	-	
Red crusted skin	-	-	-	<1	-	-	-	-	-	
Skin necrosis after extravasation	-	-	-	<1	-	-	-	-	-	
Stevens-Johnson syndrome	-	-	✔	-	-	-	<1	<1	-	
Sweating, excessive	-	≤2	2	<1	-	-	-	✔	-	
Toxic epidermal necrolysis	-	-	✔	-	-	-	<1	<1	✔	
Ulcers	-	-	✔	-	-	-	-	-	-	
Urticaria	-	-	✔	5	1 to 10	<1	-	✔	-	
Endocrine and Metabolic										

Adverse Events	Single Entity Agents (O-Z)					Combination Products				
	Penbutolol	Pindolol	Propranolol	Sotalol	Timolol	Atenolol and Chlor-thalidone	Bisoprolol and HCTZ	Metoprolol and HCTZ	Nadolol and Bendro-flumethiazide	
Diabetes (exacerbated)	-	-	-	-	-	-	-	✔	✔	
Glycosuria	-	-	-	-	-	<1	-	-	-	
Gout	-	-	-	-	-	<1	<1	-	-	
Hypoglycemia masked	-	-	-	-	1 to 10	-	-	-	-	
Libido decreased	-	-	-	-	✔	-	-	✔	-	
Gastrointestinal										
Abdominal pain	-	-	1	1 to 4	-		<1	✔	-	
Anorexia	-	-	✔	-	✔	1 to 10	1 to 10	1 to 10	✔	
Constipation	-	-	0 to 2	-	1 to 10	1 to 10	<1	1	1 to 10	
Cramping	-	-	✔	-	-				✔	
Diarrhea	1 to 10	≤2	2 to 7	2 to 7	1 to 10	1 to 10	3 to 4	5	1 to 10	
Dry mouth	-	-	-	-	✔				-	
Dyspepsia	1 to 10	-	1 to 7	2 to 3	1 to 10		<1		✔	
Epigastric distress	-	-	-	-	-	1 to 10	1 to 10	1 to 10	-	
Flatulence	-	-	4	1 to 2	-			1	-	
Gastritis/gastric irritation	-	-	-	-	-	-	<1			
Heartburn	-	-	-	-	-	-	-	1	-	
Ischemic colitis	<1	-	✔	-	-				-	
Melena	-	-	-	-	-				✔	
Nausea	1 to 10	5	1 to 6	4 to 10	1 to 10	1 to 10	2	1	1 to 10	
Pancreatitis	-	-	-	-	-	<1		<1	-	
Peptic ulcer	-	-	-	-	-	-	<1			
Periodontitis	-	-	-	-	-				✔	
Retroperitoneal fibrosis	-	-	-	-	✔			✔	-	
Stomach discomfort	-	-	✔	3 to 6	-				1 to 10	
Taste disorder	-	-	-	-	-		<1	✔	✔	
Vomiting	-	≤2	✔	4 to 10	-	<1	1 to 2	✔	1 to 10	
Weight gain	-	≤2	-	-	-		<1	✔	-	
Xerostomia	-	-	-	-	1 to 10	-	<1	-	-	
Genitourinary										
Cystitis	-	-	-	-	-	-	<1	-	-	
Impotence	-	≤2	1	2	1 to 10	1 to 10	<1	✔	-	
Interstitial nephritis	-	-	✔	-	-	-	-	-	-	
Micturition (frequency)	-	-	1	-	-	-	-	-	-	
Oliguria	-	-	✔	-	-	-	-	-	-	
Polyuria	-	≤2	-	-	-	<1	<1	-	-	
Proteinuria	-	-	✔	-	-	-	-	-	-	
Sexual ability decreased	-	-	-	3	-	-	<1	-	>10	
Hematologic										
Agranulocytosis	-	-	✔	-	-	<1	-	<1	-	
Anemia (aplastic/hemolytic)	-	-	-	-	-	<1	-	<1	✔	
Bleeding	-	-	-	2	-	-	-	-	-	
Claudication	-	-	-	-	✔	-	-	✔	-	
Eosinophilia	-	-	-	<1	-	-	-	-	-	

Adverse Events	Single Entity Agents (O-Z)					Combination Products				
	Penbutolol	Pindolol	Propranolol	Sotalol	Timolol	Atenolol and Chlor-thalidone	Bisoprolol and HCTZ	Metoprolol and HCTZ	Nadolol and Bendro-flumethiazide	
Leukopenia	-	-	-	<1	-	<1	<1	<1	<1	
Prothrombin decreased	-	-	-	-	-	-	-	-	✔	
Purpura	<1	-	✔	-	-	<1	-	-	-	
Thrombocytopenia	<1	-	✔	<1	-	<1	<1	<1	<1	
Hepatic										
Cholestatic jaundice	-	-	-	-	-	-	-	-	✔	
Hepatic impairment	-	-	-	-	-	<1	-	<1	-	
Hepatitis	-	-	-	-	-	-	-	✔	-	
Increase liver enzymes	-	7	-	-	-	<1	-	-	-	
Transaminases increase	-	-	✔	<1	-	-	<1	✔	-	
Laboratory Test Abnormalities										
Alkaline phosphatase increased	-	<1	✔	-	-	-	-	✔	-	
Electrolyte imbalance	-	-	-	-	-	-	-	-	✔	
Hypercalcemia	-	-	-	-	-	<1	-	<1	-	
Hypercholesterolemia	-	-	-	-	-	-	-	-	-	
Hyperglycemia	-	-	✔	-	-	<1	-	-	-	
Hyperkalemia	-	-	✔	-	-	-	<1	-	-	
Hyperlipidemia	-	-	✔	<1	-	-	-	-	-	
Hypernatremia	-	-	-	-	-	<1	-	-	-	
Hyperphosphatemia	-	-	-	-	-	-	-	-	✔	
Hypertriglyceridemia	-	-	-	-	-	-	<1	-	✔	
Hyperuricemia	-	<1	-	-	-	<1	<1	-	-	
Hypoglycemia	<1	-	✔	-	-	-	<1	-	-	
Hypokalemia	-	-	-	-	-	1 to 10	-	1 to 10	-	
Hyponatremia	-	-	-	-	-	<1	-	-	-	
Lactate dehydrogenase increased	-	<1	-	-	-	-	-	✔	-	
Musculoskeletal										
Arthralgia	1 to 10	7	1	-	-	-	1 to 10	✔	-	
Arthritis	-	-	-	-	-	-	-	✔	-	
Arthropathy	-	-	✔	-	-	-	-	-	-	
Asthenia	-	-	-	-		-	≤2	-	-	
Back pain	-	-	-	3	-	-	<1	-	-	
Carpal Tunnel syndrome	-	-	✔	-	-	-	-	-	-	
Extremity pain	-	-	-	7	-	-	-	-	-	
Joint pain	-	-	-	-	-	-	<1	-	-	
Muscle cramps	-	3	-	-	-	<1	<1	-	✔	
Muscle pain	-	10	-	-	-	-	<1	✔	-	
Myalgia	-	-	1	<1	-	<1	-	-	-	
Myasthenia gravis exacerbated	-	-	-	-	✔	-	-	-	-	
Myotonus	-	-	✔	-	-	-	-	-	-	
Neuralgia	-	-	-	-	-	-	-	-	✔	
Paralysis	-	-	-	<1	-	-	-	-	-	
Paresthesia	-	3	✔	4	✔	-	-	-	-	
Polyarthritis	-	-	✔	-	-	-	-	-	-	

Adverse Events	Single Entity Agents (O-Z)					Combination Products				
	Penbutolol	Pindolol	Propranolol	Sotalol	Timolol	Atenolol and Chlor-thalidone	Bisoprolol and HCTZ	Metoprolol and HCTZ	Nadolol and Bendro-flumethiazide	
Restlessness	-	-	-	-	-	<1	<1	-	-	
Tremor	-	-	-	-	-	-	<1	-	✔	
Twitching	-	-	-	-	-	-	<1	-	-	
Weakness	-	4	1	4 to 13	-	<1	-	-	✔	
Renal										
Blood urea nitrogen increase	-	-	✔	-	-	-	<1	-	-	
Creatinine increase	-	-	-	-	-	-	<1	-	-	
Hematuria	-	-	-	-	-	-	1 to 10	-	-	
Interstitial nephritis	-	-	-	-	-	-	-	<1	-	
Renal colic	-	-	-	-	-	-	<1	-	-	
Renal failure	-	-	-	-	-	-	-	<1	-	
Respiratory										
Asthma	-	-	-	1 to 2	-	-	<1	-	-	
Bronchitis	-	-	-	-	-	-	<1	-	-	
Bronchospasm	<1	-	✔	-	✔	-	<1	1	1 to 10	
Cough	<1	-	1	-	✔	-	<1	-	-	
Dyspnea	-	5	1 to 6	5 to 21	1 to 10	<1	1 to 2	1 to 3	<1	
Eosinophilic pneumonitis	-	-	-	-	-	-	-	<1	-	
Laryngospasm	-	-	✔	-	-	-	-	-	-	
Nasal congestion	-	-	-	-	✔	-	-	-	-	
Nasopharyngitis	-	-	-	-	-	-	-	-	✔	
Pharyngitis	-	-	✔	-	-	-	<1	-	-	
Pulmonary edema	-	-	✔	<1	✔	-	-	-	-	
Respiratory failure	-	-	✔	-	✔	-	-	<1	-	
Rhinitis	-	-	1	-	-	-	3 to 4	✔	-	
Sinusitis	-	-	-	-	-	-	2	-	-	
Upper respiratory infection	-	-	5	5 to 8	-	-	5	-	-	
Wheezing	-	≤2	✔	-	-	<1	-	1	✔	
Special Senses										
Abnormal/blurred vision	-	-	3	-	-	-	-	✔	-	
Burning	-	≤2	-	-	-	-	-	-	-	
Corneal sensitivity decrease	-	-	-	-	✔	-	-	-	-	
Cystoid macular edema	-	-	-	-	✔	-	-	-	-	
Diplopia	-	-	-	-	✔	-	-	-	-	
Dry eyes	-	-	-	-	✔	-	-	✔	-	
Eye discomfort/pain	-	≤2	-	-	-	-	<1	-	-	
Hearing decreased	-	-	-	-	-	-	<1	-	-	
Hyperemia of conjunctiva	-	-	✔	-	-	-	-	-	-	
Keratitis	-	-	-	-	1 to 10	-	-	-	-	
Lacrimation abnormal	-	-	-	-	-	-	<1	-	✔	
Mydriasis	-	-	✔	-	-	-	-	-	-	
Ocular discharge	-	-	-	-	✔	-	-	-	-	
Ocular pain	-	-	-	-	✔	-	-	-	-	
Ptosis	-	-	-	-	✔	-	-	-	-	

Adverse Events	Single Entity Agents (O-Z)					Combination Products				
	Penbutolol	Pindolol	Propranolol	Sotalol	Timolol	Atenolol and Chlor-thalidone	Bisoprolol and HCTZ	Metoprolol and HCTZ	Nadolol and Bendro-flumethiazide	
Refractive changes	-	-	-	-	✔	-	-	-	-	
Tinnitus	-	-	-	-	1 to 10	-	<1	-	-	
Visual disturbances	-	≤2	✔	1 to 5	✔	-	<1	✔	-	
Xerophthalmia	-	-	✔	-	-	-	-	-	-	
Other										
Allergy	-	-	-	-	✔	-	-	<1	-	
Anaphylactoid reaction	-	-	✔	-	-	-	-	-	-	
Angioedema	-	-	-	-	1 to 10	-	-	-	✔	
Cholecystitis	-	-	-	-	-	<1	-	-	-	
Cutaneous vasculitis	-	-	-	-	-	<1	<1	-	-	
Gangrene	-	-	-	-	-	-	-	✔	-	
Hypervolemia	-	-	-	-	-	-	-	-	✔	
Lupus syndrome	-	-	✔	-	1 to 10	<1	-	-	✔	
Mesenteric arterial thrombosis	<1	-	-	-	-	-	-	-	-	
Necrotizing angitis	-	-	-	-	-	<1	-	-	-	
Peyronie's disease	-	-	✔	-	1 to 10	<1	<1	<1	-	
Positive antinuclear antibody test	-	-	-	-	-	<1	<1	-	-	
Tinnitus	-	-	-	-	-	-	-	✔	-	

✔ Percent not specified
- Event not reported

Table 10. Boxed Warning for Atenolol[1]

WARNING
Advise patients with coronary artery disease who are being treated with atenolol against abrupt discontinuation of therapy. Severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias have been reported in patients with angina following the abrupt discontinuation of therapy with β-blockers. The last two complications may occur with or without preceding exacerbation of the angina pectoris. As with other β-blockers, when discontinuation of atenolol is planned, observe the patient carefully and advise the patient to limit physical activity to a minimum. If the angina worsens or acute coronary insufficiency develops, it is recommended that atenolol be promptly reinstituted, at least temporarily. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue atenolol therapy abruptly, even in patients treated only for hypertension.

Table 11. Boxed Warning for Metoprolol[1]

WARNING
Ischemic heart disease: Following abrupt cessation of therapy with certain β-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered metoprolol, particularly in patients with ischemic heart disease, gradually reduce the dosage over a period of one to two weeks and carefully monitor the patient. If angina markedly worsens or acute coronary insufficiency develops, reinstate metoprolol administration promptly, at least temporarily, and take other measures appropriate for the management of unstable angina. Warn patients against interruption or discontinuation of therapy without their health care provider's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue metoprolol tartrate therapy abruptly, even in patients treated only for hypertension.

Table 12. Boxed Warning for Nadolol[1]

WARNING
Exacerbation of ischemic heart disease following abrupt withdrawal: Hypersensitivity to catecholamines has been observed in patients withdrawn from β-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after abrupt discontinuation of such therapy. When discontinuing chronically administered nadolol, particularly in patients with ischemic heart disease, gradually reduce the dosage over a period of one to two weeks and carefully monitor the patient. If angina markedly worsens or acute coronary insufficiency develops, reinstitute nadolol administration promptly, at least temporarily, and take other measures appropriate for the management of unstable angina. Warn patients against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly, even in patients treated only for hypertension.

Table 13. Boxed Warning for Propranolol[1]

WARNING
Angina pectoris: There have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of propranolol therapy. Therefore, when discontinuance of propranolol is planned, the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without a health care provider's advice. If propranolol therapy is interrupted and exacerbation of angina occurs, it is usually advisable to reinstitute propranolol therapy and take other measures appropriate for the management of angina pectoris. Because coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Table 14. Boxed Warning for Sotalol[1]

WARNING
To minimize the risk of induced arrhythmia, place patients initiated or reinitiated on sotalol AF or sotalol for a minimum of three days (on their maintenance dose) in a facility that can provide cardiac resuscitation, continuous electrocardiographic monitoring, and calculations of creatinine clearance. Calculate creatinine clearance prior to dosing. Do not substitute sotalol for sotalol AF because of significant differences in labeling (i.e., patient package insert, dosing administration, safety information).

Table 15. Boxed Warning for Timolol[1]

WARNING
Exacerbation of ischemic heart disease following abrupt withdrawal: Hypersensitivity to catecholamines has been observed in patients withdrawn from β-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after abrupt discontinuation of such therapy. When discontinuing chronically administered timolol, particularly in patients with ischemic heart disease, gradually reduce the dosage over a period of one to two weeks and carefully monitor the patient. If angina markedly worsens or acute coronary insufficiency develops, reinstitute timolol administration promptly, at least temporarily, and take other measures appropriate for the management of unstable angina. Warn patients against interruption of discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue timolol therapy abruptly, even in patients treated only for hypertension.

VII. Dosing and Administration

The usual dosing regimens for the β-adrenergic blocking agents are listed in Table 16.

Table 16. Usual Dosing Regimens for the Beta-Adrenergic Blocking Agents[1-3]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Acebutolol	Hypertension: Capsule: initial, 400 mg/day, twice daily dosing may be required for adequate control; maintenance, 200 to 1,200 mg/day in two divided doses; maximum, 1,200 mg/day Ventricular arrhythmias: Capsule: initial: 200 mg twice daily; maintenance, gradual increase until optimal response, usually 600 to 1,200 mg/day; maximum, 1,200 mg/day	Safety and efficacy in children have not been established.	Capsule: 200 mg 400 mg
Atenolol	Angina pectoris: Tablet: initial, 50 mg once daily; maintenance, if optimal response not achieved after one week, increase to 100 mg daily; maximum, 200 mg/daily Hypertension: Tablet: initial: 50 mg once daily; maintenance, if optimal response not achieved, increase dose to 100 mg once daily; maximum, 100 mg/day Myocardial infarction:	Safety and efficacy in children have not been established.	Tablet: 25 mg 50 mg 100 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Tablet: 50 mg twice daily, or 100 mg once daily for 6 to 9 days or until hospital discharge		
Betaxolol	Hypertension: Tablet: initial, 10 mg once daily; maintenance, if optimal response not seen after seven to 14 days, may increase the dose to 20 mg/day; maximum, 40 mg/day	Safety and efficacy in children have not been established.	Tablet: 10 mg 20 mg
Bisoprolol	Hypertension: Tablet: initial, 2.5 to 5 mg once daily; maintenance, if optimal control is not achieved, dose may be increased to 10 mg daily and again to 20 mg/day if needed; maximum, 20 mg/day	Safety and efficacy in children have not been established.	Tablet: 5 mg 10 mg
Carvedilol	Heart failure: Extended-release capsule: initial, 10 mg once daily; maintenance, if tolerated, double the dose at intervals of >14 days as needed; maximum, 80 mg once daily Tablet: initial, 3.125 mg twice daily; maintenance, if tolerated, double the dose at intervals of >14 days as needed up to 50 mg twice daily; maximum, 25 mg twice daily (patients ≤85 kg) or 50 mg twice daily (patients >85 kg) Hypertension: Extended-release capsule: initial, 20 mg once daily; maintenance, if tolerated, double the dose every seven to 14 days as needed; maximum, 80 mg once daily Tablet: initial, 6.25 mg twice daily; maintenance, if tolerated, double the dose every seven to 14 days as needed; maximum, 25 mg twice daily Myocardial Infarction: Capsule ER: initial, 10 to 20 mg once daily; maintenance: if tolerated, double the dose every 3 to 10 days as needed up to a maximum of 80 mg once daily Tablet IR: initial, 6.25 mg twice daily; maintenance: if tolerated, double the dose every 3 to 10 days as needed up to a maximum of 25 mg twice daily	Safety and efficacy in children have not been established.	Extended-release capsule: 10 mg 20 mg 40 mg 80 mg Tablet: 3.125 mg 6.25 mg 12.5 mg 25 mg
Labetalol	Hypertension: Injection, tablet: initial: 100 mg twice daily; maintenance, titrate by increments of 100 mg twice daily every two to three days, usual dose is 200 to 400 mg twice daily; larger doses may be administered three times daily to improve tolerability;	Safety and efficacy in children have not been established.	Injection: 5 mg/mL Tablet: 100 mg 200 mg 300 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	maximum, doses of 1,200 to 2,400 mg/day have been used		
Metoprolol	Angina pectoris: Extended-release capsule, tablet: initial, 100 mg once daily; maintenance, gradually increase dose in weekly intervals; maximum, 400 mg/day Injection, tablet: initial, 100 mg/day in two divided doses; maintenance, gradually increase dose in weekly intervals, usual dose is 100 to 400 mg/day; maximum, 400 mg/day Heart failure: Extended-release capsule, tablet: initial, 25 mg/day; maintenance, double the dose every two weeks up to 200 mg/day or highest dose tolerated Hypertension: Extended-release capsule, tablet: initial, 25 to 100 mg once daily; maintenance, gradually increase dose in weekly intervals up to 400 mg/day Injection, tablet: initial, 50 to 100 mg/day in single or divided doses; maintenance, gradually increase dose in weekly intervals, usual dose is 100 to 450 mg/day; maximum, 450 mg/day Myocardial infarction: Injection, tablet: initial, 100 mg twice daily; maintenance, 100 mg twice daily for at least three months	Hypertension in children ≥6 years of age: Extended-release capsule, tablet: initial: 1 mg/kg once daily (maximum: 50 mg once daily); maintenance, adjust dose to optimal response up to 2 mg/kg or 200 mg/day; maximum, 2 mg/kg/day or 200 mg/day Safety and efficacy in children <6 years of age have not been established.	Extended-release capsule (succinate): 25 mg 50 mg 100 mg 200 mg Extended-release tablet (succinate): 25 mg 50 mg 100 mg 200 mg Injection (tartrate): 5 mg/5 mL Tablet (tartrate): 25 mg 37.5 mg 50 mg 75 mg 100 mg
Nadolol	Angina pectoris: Tablet: initial, 40 mg once daily; maintenance, increase dose by 40 to 80 mg every three to seven days until optimal response; maximum, 240 mg/day Hypertension: Tablet: initial, 40 mg once daily; maintenance, increase dose gradually by 40 to 80 mg increments every seven to 21 days until optimal response; maximum, 320 mg/day	Safety and efficacy in children have not been established.	Tablet: 20 mg 40 mg 80 mg
Nebivolol	Hypertension: Tablet: initial: 5 mg once daily; maintenance, increase in two week intervals until optimal response; maximum, 40 mg/day	Safety and efficacy in children have not been established.	Tablet: 2.5 mg 5 mg 10 mg 20 mg
Penbutolol	Hypertension: Tablet: initial, 20 mg once daily;	Safety and efficacy in children have not been	Tablet: 20 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	maintenance, 20 mg once daily, usual dose 10 to 40 mg once daily; maximum, 80 mg/day	established.	
Pindolol	Hypertension: Tablet: initial, 5 mg twice daily; maintenance, after three to four weeks, may be increase by 10 mg/day increments as needed; maximum, 60 mg/day	Safety and efficacy in children have not been established.	Tablet: 5 mg 10 mg
Propranolol	Angina pectoris: Extended-release capsule (Inderal LA®): initial, 80 mg once daily; maintenance, may gradually increase dose in three to seven day increments up to 160 mg once daily or higher, usual dose is 160 mg daily; maximum, 320 mg/day Solution, tablet: maintenance, 80 to 320 mg/day administered in two, three or four divided doses; maximum, 320 mg/day Cardiac arrhythmias: Injection (ventricular arrhythmias): usual dose, 1 to 3 mg Solution, tablet (atrial fibrillation): maintenance, 10 to 30 mg in three to four divided doses before meals and at bedtime Essential tremor: Solution, tablet: initial, 40 mg twice daily; maintenance, usual dose is 120 mg/day; maximum, 320 mg/day Hypertension: Extended-release capsule (Inderal LA®): initial, 80 mg once daily; maintenance, may titrate dose up to 120 mg/day or higher, usual dose is 120 to 160 mg/day; maximum, 640 mg/day Extended-release capsule (InnoPran XL®): initial, 80 mg once daily at bedtime (around 10 pm); maintenance, may titrate dose up to 120 mg/day; maximum, 120 mg/day Solution, tablet: initial, 40 mg twice daily; maintenance, gradually increase the dose up to 640 mg/day divided into two to three doses, usual dose is 120 to 240 mg/day divided into two to three doses; maximum, 640 mg/day Hypertrophic subaortic stenosis: Extended-release capsule (Inderal LA®):	Infantile hemangioma: Solution (Hemangeol®): Initiate treatment at 5 weeks to 5 months; initial, 0.15 mL/kg (0.6 mg/kg) twice daily at least 9 hours apart; after one week increase to 0.3 mL/kg (1.1 mg/kg) twice daily; after another week increase the dose to 0.4 mL/kg (1.7 mg/kg) twice daily and maintain for six months, readjusting for weight changes Safety and effectiveness for infantile hemangioma have not been established in pediatric patients greater than one year of age	Extended-release capsule: 60 mg 80 mg 120 mg 160 mg Injection: 1 mg/mL Solution: 4.28 mg/mL 20 mg/5 mL 40 mg/5 mL Tablet: 10 mg 20 mg 40 mg 60 mg 80 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	maintenance, 80 to 160 mg once daily Solution, tablet: 20 to 40 mg three to four times daily before meals and at bedtime Migraine: Extended-release capsule (Inderal LA®): initial, 80 mg once daily; maintenance, may increase dose gradually up to 160 to 240 mg once daily, usual dose is 160 to 240 mg once daily; maximum, 240 mg/day Solution, tablet: initial, 80 mg daily in divided doses; maintenance, increase dose gradually up to 160 to 240 mg/day; maximum, 240 mg/day Myocardial Infarction: Solution, tablet: initial, 40 mg three times daily; maintenance, after one month, titrate up to 60 to 80 mg three times daily as tolerated, usual dose is 180 to 240 mg in divided doses; maximum, 240 mg/day Pheochromocytoma: Solution, tablet (operable tumors): 60 mg/day in divided doses for three days preoperatively as adjunct to α-adrenergic blockade Solution, tablet (inoperable tumors): 30 mg/day in divided doses as adjunct to α-adrenergic blockade		
Sotalol	Cardiac arrhythmias: Solution, tablet (Betapace AF®, Sotylize®; maintenance of normal sinus rhythm): initial, 80 mg twice daily; maintenance, increase dose gradually with three days between increments up to 120 mg twice daily; maximum, 160 mg twice daily Solution, tablet (Betapace®, Sotylize®; ventricular arrhythmias): initial, 80 mg twice daily; maintenance, increase dose gradually with three days between increments up to 120 to 160 mg twice daily; maximum, 480 to 640 mg/day	Cardiac arrhythmias in children >2 years of age: Solution, tablet (Betapace AF®, Sotylize®; maintenance of normal sinus rhythm): initial, 30 mg/m^2 three times daily; maintenance, increase dose gradually with three days between increments up to 60 mg/m^2 three times daily; maximum, 60 mg/m^2 three times daily; neonate dosing available for Sotylize® Solution, tablet (Betapace®, Sotylize®; ventricular Arrhythmias): initial,	Solution: 5 mg/mL Tablet: 80 mg 120 mg 160 mg 240 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		30 mg/m^2 three times daily; maintenance, increase dose gradually with three days between increments up to 60 mg/m^2 three times daily; maximum, 60 mg/m^2 three times daily; neonate dosing available for Sotylize®	
Timolol	Hypertension: Tablet: initial, 10 mg twice daily; maintenance, increase dose gradually in seven day increments up to 60 mg/day, usual dose is 20 to 40 mg/day; maximum, 60 mg/day divided into two doses Migraine: Tablet: initial, 10 mg twice daily; maintenance, may increase dose up to 30 mg/day; maximum, 30 mg/day divided into two doses Myocardial infarction: Tablet: 10 mg twice daily	Safety and efficacy in children have not been established.	Tablet: 5 mg 10 mg 20 mg
Combination Products			
Atenolol and chlorthalidone	Hypertension: Tablet: initial: 50-25 mg once daily; maintenance, if optimum response is not achieved after one to two weeks, may increase to 100-25 mg once daily	Safety and efficacy in children have not been established.	Tablet: 50-25 mg 100-25 mg
Bisoprolol and HCTZ	Hypertension: Tablet: initial, 2.5-6.25 mg once daily; maintenance, may titrate dose every seven to 14 days; maximum, 20-12.5 mg once daily	Safety and efficacy in children have not been established.	Tablet: 2.5-6.25 mg 5-6.25 mg 10-6.25 mg
Metoprolol and HCTZ	Hypertension: Extended-release tablet: dosing must be individualized, the usual dose of metoprolol is 25 to 100 mg/day, and the usual dose of HCTZ is 12.5 to 50 mg/day Tablet: initial, 100-25 mg/day in single or divided doses; maintenance, may titrate dose gradually until desired effect is achieved, usual dose of metoprolol is 100 to 450 mg/day, and usual dose of HCTZ is 12.5 to 50 mg/day, may be administered in single or divided doses	Safety and efficacy in children have not been established.	Tablet: 50-25 mg 100-25 mg 100-50 mg
Nadolol and bendro-flumethiazide	Hypertension: Tablet: initial, 40-5 mg once daily; maintenance, if desired effect is not achieved, may increase dose to 80-5 mg once daily	Safety and efficacy in children have not been established.	Tablet: 80-5 mg

HCTZ=hydrochlorothiazide, NYHA=New York Heart Association

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the β-adrenergic blocking agents are summarized in Table 17.

Table 17. Comparative Clinical Trials with the Beta-Adrenergic Blocking Agents

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Angina				
Pandhi et al.[39] (1985) Acebutolol 100 to 400 mg TID vs propranolol 40 to 160 mg TID vs placebo	DB, XO Patients with classical anginal symptoms of effort with ≥7 attacks per week and angina being stable for ≥8 to 12 weeks	N=24 18 weeks	Primary: Incidence of anginal attack, number of nitroglycerin tablets used, exercise tolerance, side effects Secondary: Not reported	Primary: Both acebutolol and propranolol significantly reduced the incidence of anginal attacks per week compared to placebo (P<0.001 for both groups), but the difference between the two groups was not significant (P>0.05). Both acebutolol and propranolol significantly reduced the number of nitroglycerin tablets used per week compared to placebo (P<0.001 for both groups), but the difference between the two groups was not significant (P>0.05). Both acebutolol and propranolol significantly improved exercise tolerance compared to placebo (P<0.001), but the difference between the two groups was not significant (P>0.05). Side effects reported (i.e., insomnia, sweating, bitter taste, heart burn, muscle weakness) were similar between the two treatment groups. Clinical significance of the side effects was not reported. Secondary: Not reported
Jackson et al.[40] (1980) Atenolol 25, 50, 100, and 200 mg/day, each dose administered for a 2 week period vs	XO Adult patients with clinically stable exercise-induced angina for ≥3 months	N=10 12 weeks	Primary: Anginal attack rate, nitroglycerin consumption, exercise data Secondary: Not reported	Primary: Compared to placebo, atenolol reduced the angina attack rate during all periods (P<0.001). A dose response was present with a decreasing number of attacks with increasing dosage. Doses of 100 and 200 mg were significantly more effective to 25 mg (P<0.001 for both), but there was no significant difference between the 50 and 100 mg, or 100 and 200 mg (P values not reported). Nitroglycerin consumption declined in a parallel, dose-related fashion. Compared to placebo, all doses of atenolol decreased nitroglycerin consumption significantly (P<0.001), with no significant difference

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo All patients received SB placebo for the first 4 weeks of the trial.				between 50 vs 100 and 200 mg, or 100 vs 200 mg (P values not reported). All doses of atenolol significantly reduced resting and exercise heart rate at three hours (P<0.001) and 24 hours (P<0.001) after ingestion. Atenolol was significantly more effective at 100 and 200 mg, with no significant difference between the two doses (P value not reported). The maximal exercise double product (heart rate times SBP) at the occurrence of chest pain was significantly reduced at peak and trough testing with all atenolol doses (P<0.001 for all), but 100 and 200 mg were significantly more effective than 25 and 50 mg (P<0.001 for both). The amount of exercise necessary to produce angina three hours after drug ingestion was increased by all atenolol doses; however, only 50 (P<0.001), 100 (P<0.005) and 200 mg (P<0.001) showed significant improvement compared to placebo. Secondary: Not reported
Oh et al.[41] (2016) Atenolol 25 mg BID vs carvedilol 12.5 mg BID After a week of treatment, the initial dose of the study medication could be doubled	OL, PG, PRO, RCT Patients 20 to 80 years of age with stable angina pectoris who had a positive exercise treadmill test according to American College of Cardiology Foundation and American Heart Association guidelines	N=89 6 months	Primary: BP, heart rate, treadmill exercise test, Seattle Angina Questionnaire, metabolic parameters Secondary: Not reported	Primary: Office SBP and DBP at baseline was similar between the two groups and had not changed at the end of the study. Both carvedilol and atenolol significantly reduced heart rate from baseline (76 ± 11 to 66 ± 9 beat/min, P<0.001; 74 ± 9 to 64 ± 9 beat/min, P<0.001, respectively). Improvement of time to ST-segment depression during the treadmill exercise and the Seattle Angina Questionnaire scores for angina stability and frequency after six months of treatment were similar between groups. There was no significant change from baseline in the level of fasting glucose, insulin, or glycated hemoglobin in either group. However, TC and LDL-C levels significantly reduced to a greater extent with carvedilol than with atenolol (−23 vs −10 and –38 vs –24%, respectively, P<0.05 for both), although the rate of statin use was comparable. No changes were seen in HDL cholesterol and triglyceride levels after six months of treatment in both groups compared with baseline. Secondary: Not reported
Kardas et al.[42] (2007)	OL, PG, RCT Patients 40 to 75	N=112 8 weeks	Primary: Overall compliance	Primary: The overall compliance significantly higher in the betaxolol group compared to the metoprolol group (86.5±21.3 vs 76.1±26.3%,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Betaxolol 20 mg QD vs metoprolol 50 mg BID	years with ischemic heart disease NYHA class I to II, no prior β-blocker treatment, and whose mental state enabled conscious participation in the study		Secondary: Drug effectiveness, health-related QOL	respectively; P=0.002). Secondary: There was not a significant difference in chest pain episodes observed between the betaxolol and metoprolol groups compared from baseline (0.42/week and 0.46/week change in episodes, respectively; P>0.05). Overall, QOL dimensions were similar among both treatment groups, with the exception of physical function in which a significantly greater improvement was observed in the betaxolol group compared to the metoprolol group (42.9 vs 15.2 patients improved, respectively; P<0.01).
van der Does et al.[43] (1999) Carvedilol 25 to 50 mg BID vs metoprolol 50 to 100 mg BID	DB, MC, RCT Patients ≤80 years of age with CHD and chronic stable angina for ≥2 months, exertional angina with symptoms improving after taking short acting nitrates or after a period of rest, and 1 exercise test performed that was limited by moderate anginal pain	N=368 3 months	Primary: Moderate anginal pain and time to ST- 1-mm segment depression Secondary: Not reported	Primary: Compared to baseline, both carvedilol and metoprolol significantly decreased time to anginal pain during exercise test (+77s [+20 to +140] and +76 [+25 to +155], respectively; P<0.001 for both). Compared to baseline, both carvedilol and metoprolol significantly decreased time to ST- 1-mm segment depression during exercise test (+75.5 s [+47 to +154 s] and +60 [0 to +146 s], respectively; P<0.001 for both). Carvedilol significantly improved the time to 1-mm ST-segment depression compared to metoprolol (RR, 1.386; 95% CI, 1.045 to 1.839; P<0.05) Secondary: Not reported
Weiss et al.[44] (1998) Carvedilol 12.5 to 50 mg BID vs placebo	DB, MC, XO Patients with 2 stress tests which evoked ischemic signs and symptoms	N=122 12 weeks	Primary: Efficacy, safety Secondary: Not reported	Primary: The carvedilol 25 and 50 mg groups significantly reduced the time to angina compared to placebo (25 mg: 337 s, P=0.0039; 50 mg: 345 s; P<0.001 vs 316 s). The carvedilol 25 and 50 mg groups significantly reduced the time to 1-mm ST-segment depression compared to placebo (25 mg: 313 s; 50 mg: 323 s vs 301 s; P<0.0001 for both).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The percentage of patients reporting any adverse experience was slightly less in those receiving placebo (placebo: 28.4%; 12.5 mg: 33.1%; 25 mg: 34.5%; 50 mg: 31.9%). Adverse events included dizziness, fatigue, headache, dyspepsia, and any hypotensive event. The clinical significance of the adverse events was not reported. Secondary: Not reported
Hauf-Zachariou et al.[45] (1997) Carvedilol 25 mg BID vs verapamil 120 mg TID	DB, MC, PG, RCT Patients 18 to 75 years with a confirmed diagnosis of CAD, exertional chest pain relieved by rest or glyceryl trinitrate for ≥2 months and 2 exercise tests with signs and symptoms of ischemia	N=313 12 weeks	Primary: Total exercise time, time to onset of angina, and time to 1 mm ST-segment depression, blood pressure, heart rate, rate pressure product Secondary: Not reported	Primary: There was not a significant difference in total exercise time observed between the carvedilol (increased from 378 s to 436 s) and verapamil (increased from 386 s to 438 s) groups (RR, 1.14; 90% CI, 0.85±1.52). There was not a significant difference observed between the carvedilol and verapamil groups in time to onset of angina (increase from 296 s to 325 s vs 285 s to 326 s) and in time to 1 mm ST-segment depression (increase from 267 s to 298 s vs 286 s to 302 s). At peak exercise and at maximum comparable workload, carvedilol significantly reduced SBP (from 175 to 166 mm Hg) compared to verapamil (from 173 to 173 mm Hg)). At peak exercise and at maximum comparable workload, carvedilol significantly reduced heart rate (from 123 to 112 mm Hg) compared to verapamil (from 124 to 120 mm Hg)). At peak exercise and at maximum comparable workload, carvedilol significantly reduced rate pressure product (from 21564 to 18802 mm Hg) compared to verapamil (from 21488 to 20992 mm Hg)). Secondary: Not reported
Savanitto et al.[46] (1996) <u>Weeks 1 to 6</u>: Metoprolol ER	DB, MC, RCT Patients with typical anginal symptoms that had been stable	N=280 6 weeks	Primary: Angina frequency, exercise tolerance, safety	Primary: At week six, both metoprolol (mean change, -1.95; 95 % CI, -1.25 to -2.64) and nifedipine (mean change, -1.57; 95 % CI, -0.69 to -2.45) significantly reduced the frequency of angina compared to baseline, but there was not a statistical difference between groups. At the end of 10

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
200 mg QD vs nifedipine 20 mg BID <u>Weeks 7 to 10</u>: Metoprolol ER 200 mg QD plus placebo vs metoprolol ER 200 mg QD and nifedipine 20 mg BID vs nifedipine 20 mg BID plus placebo	for approximately 6 months, who showed a positive response to exercise stress testing with 23 min of exercise tolerance and were in sinus rhythm and had an analyzable ST segment on ECG		Secondary: Not reported	weeks, there was not a statistical difference observed between the groups. At week six, both metoprolol and nifedipine significantly increased the mean exercise time to l-mm ST-segment depression compared to baseline (both P<0.01); but metoprolol was significantly more effective than nifedipine (P<0.05). At week 10, the groups randomized to combination therapy had a further increase in time to l-mm ST-segment depression (P<0.05 vs placebo). There were 14 cardiovascular events including one sudden death, three acute myocardial infarctions, eight cases of unstable angina, one of syncope and one of stroke and the incidence of these events did not differ among the treatment groups. Secondary: Not reported
Turner et al.[47] (1978) Propranolol 40 to 240 mg/day, administered in 4 divided doses vs nadolol 40 to 240 mg/day, administered in 2 divided doses	DB, PC, RCT, XO Men with ischemic heart disease with presence of stable angina pectoris and absence of acute MI during the preceding 4 months, ECG evidence of myocardial ischemia during treadmill exercise testing and/or	N=14 Up to 18 weeks	Primary: Glyceryl trinitrate consumption, exercise tolerance, heart rate Secondary: Not reported	Primary: Mean glyceryl trinitrate consumption decreased significantly from placebo with both propranolol and nadolol (P<0.05 for all). There was no significant difference between propranolol and nadolol, with nadolol 240 mg/day producing a significant decrease in consumption of glyceryl trinitrate compared to 160 mg/day (P<0.05). Both treatments resulted in similar improvements in exercise tolerance (30%; P<0.01) and external work performed (48%; P<0.01). A slightly greater suppression of heart rate during exercise was observed with nadolol compared to propranolol (P<0.05). Both treatments resulted in significant decreases in resting heart rate;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	arteriographic evidence of >60% obstruction of the lumen of ≥2 major coronary arteries, the absence of CHF, a resting DBP <90 mm Hg, absence of contra- indications to β-blocker therapy and the absence of other cardiac or severe systemic disease			however, the rate corrected systolic time intervals changed very little from control. The effects of the two treatments could not be differentiated by echocardiography or phonocardiography. Secondary: Not reported
Arrhythmias				
Lui et al.[48] (1983) Acebutolol 200 or 400 mg/day vs placebo	DB, PC, RCT, XO Adult patients with ≥30 ventricular ectopic beats per hour on 3 control ambulatory monitoring	N=25 Not reported	Primary: Resting heart rate, ventricular arrhythmias, paired ventricular ectopic beats, ventricular tachycardia, electro-physiologic effects, adverse events Secondary: Not reported	Primary: Both doses of acebutolol produced a significant decrease in heart rate (P<0.01 for both), with no significant differences between 200 and 400 mg (P value not reported). Mean ventricular ectopic beat reduction from the control period was 34.9% during the two placebo periods. Following acebutolol, mean ectopic beat suppression was greater, although not significantly different when compared to placebo, at 44.9 and 49.5% using 200 and 400 mg, respectively (P values not reported). Nineteen of the 25 patients achieved episodes of paired ventricular ectopic beats (couplets) on control ambulatory monitoring. The mean reduction of paired beats was significantly higher than placebo (48.8%) with 70.5 (P<0.05) and 74.5% (P<0.01) with acebutolol 200 and 400 mg, respectively. Five patients who had ventricular tachycardia during both control and placebo periods had complete suppression during acebutolol treatment. Mean QRS and QTc intervals revealed no significant difference as compared to the control period.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There were no significant adverse effects related to acebutolol administration. Patients did not develop any bronchospasm, significant bradycardia, heart block, CHF or any central nervous system adverse effect. Secondary: Not reported
Lee et al.[49] (2008) Amiodarone vs sotalol vs β-blockers (agents not specified) Doses of the agents were not specified	RETRO Patients with AF and/or CHF (NYHA class ≥III) and an implantable cardioverter defibrillator	N=55 2.6 years	Primary: Cumulative rates of inappropriate shocks Secondary: Not reported	Primary: Amiodarone demonstrated a significantly lower rate of inappropriate shock was compared β-blocker group (27.3 vs 70.6% at four years; P=0.003). This demonstrated an 83% reduction compared to the β-blockers (HR, 0.17; 95% CI, 0.05 to 0.64; P=0.008). There was not a significant difference in rates of inappropriate shocks observed between the amiodarone and sotalol groups (27.3 vs 54.3% at four years; P=0.29). There was not a significant difference in rates of inappropriate shocks observed between the sotalol and β-blocker groups (54.3 vs 70.6% at four years; P=0.16). Secondary: Not reported
Connolly et al.[50] (2006) OPTIC β-blocker (bisoprolol, carvedilol or metoprolol) vs sotalol 240 mg/day	DB, MC, RCT Patients who received an implantable cardioverter defibrillator within 21 days of randomization, had sustained ventricular tachycardia,	N=412 12 months	Primary: Implantable cardioverter defibrillator shock for any reason Secondary: Not reported	Primary: Shocks occurred in 41 patients (38.5%) in the β-blocker group, 26 (24.3%) in the sotalol group, and 12 (10.3%) in the amiodarone plus β-blocker group. A reduction in the risk of shock was observed with use of amiodarone plus β-blocker or sotalol vs β-blocker alone (HR, 0.44; 95% CI, 0.28 to 0.68; P<0.001). The amiodarone plus β-blocker group significantly reduced the risk of shock compared to β-blocker alone (HR, 0.27; 95% CI, 0.14 to 0.52; P<0.001) and sotalol (HR, 0.43; 95% CI, 0.22 to 0.85; P=0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
in two to three divided doses vs amiodarone 200 mg QD plus β-blocker (bisoprolol, carvedilol or metoprolol) Amiodarone was loaded at 400 mg BID for 2 weeks, followed by 400 mg/day for 4 weeks, and then 200 mg/day until then end of the study	ventricular fibrillation or cardiac arrest, LVEF ≤40%, inducible ventricular tachycardia or ventricular fibrillation by programmed ventricular stimulation with LVEF ≤40% or unexplained syncope with ventricular tachycardia or ventricular fibrillation, inducible by programmed stimulation			Sotalol did not significantly reduce the risk of shock compared to the β-blocker alone group (HR, 0.61; 95% CI, 0.37 to 1.01; P=0.055). Secondary: Not reported
Balcetyte-Harris et al.[51] (2002) Esmolol 0.5 mg/kg over 5 minutes then 0.05 mg/kg/min titrated to heart rate of 55 to 65 bpm and SBP >100 mm Hg for up to 24 hours vs	OL, RCT Patients referred for elective CABG without concomitant valve replacement who were in sinus rhythm	N=50 72 hours	Primary: Development of AF lasting >30 mins Secondary: Development of adverse events, hypotension (SBP <90 mm Hg), symptomatic bradycardia or CHF (left ventricular failure)	Primary: There was not a significant difference in development of AF after CABG between the esmolol and β-blocker group (seven [26%] vs six [26%] patients, respectively). Secondary: Significantly more patients in the esmolol group experienced significant adverse events compared to the patients in the β-blocker group (11 [41%] vs one [4%] patient(s), respectively; P=0.006). Significantly more patients in the esmolol group experienced hypotension compared to the patients in the β-blocker group (eight vs one patient(s), respectively; P=0.03). There was not a statistically significant difference between the esmolol

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
oral β-blocker (metoprolol ≥50 mg/day was the preferred agent)				and the β-blocker group in the development bradycardia requiring pacing (two vs zero patients, respectively) and in left ventricular failure (one vs zero patient(s), respectively).
Kettering et al.[52] (2002) Metoprolol 25 to 200 mg/day vs sotalol 40 to 480 mg/day	PRO, RCT Symptomatic patients between 18 and 80 years with sustained ventricular tachycardia and/or ventricular fibrillation requiring an implantable cardioverter defibrillator	N=100 2 years	Primary: Ventricular tachycardia or ventricular fibrillation recurrence requiring implantable cardioverter defibrillator intervention Secondary: Total mortality	Primary: There was not a significant difference in ventricular tachycardia/ ventricular fibrillation recurrence rates observed between the metoprolol group (33 patients) and the sotalol group (30 patients; P=0.68). After one year of treatment, 46.3% of patients in the metoprolol group and 54.7% of patients in the sotalol group were free of a recurrence of ventricular tachycardia or ventricular fibrillation (P=0.68). After two years, rates were 31.5 and 36.6%, respectively. Secondary: There was not a significant difference in mortality rates observed between the metoprolol group (eight deaths) and the sotalol group (six patients; P=0.43).
Seidl et al.[53] (1998) Metoprolol 50 mg/day vs sotalol 80 mg/day The doses of the study medications were titrated to the maximum titrates dose.	OL, RCT Patients >18 years of age requiring treatment if life-threatening ventricular tachycardia/ ventricular fibrillation who required an implantable cardioverter defibrillator due to non-inducible or drug refractory (≥1 unsuccessful antiarrhythmic trial) arrhythmias	N=70 26±16 months	Primary: Recurrence of ventricular tachycardia requiring antitachycardia pacing, fast ventricular tachycardia or ventricular fibrillation requiring implantable cardioverter defibrillator, discharges, total mortality Secondary:	Primary: Actuarial rates for absence of ventricular tachycardia recurrence were significantly higher in the metoprolol group vs the sotalol group at one and two years (83 and 80 vs 57 and 51%, respectively; P=0.016). Actuarial rates for absence of recurrence of a fast ventricular tachycardia or ventricular fibrillation were significantly higher in the metoprolol group vs the sotalol group one and two years (88 and 80 vs 54 and 46%, respectively; P=0.002) Actuarial survival rates at one and two years were not significantly different between the metoprolol and sotalol groups (94 and 91 vs 86 and 83%, respectively; P=0.287) Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Not reported	
Steeds et al.[54] (1999) Sotalol 80 mg BID vs atenolol 50 mg QD	OL, PRO, RCT, XO Symptomatic patients >50 years of age with paroxysmal AF documented on ECG	N=47 2 months	Primary: Frequency of paroxysmal AF Secondary: Average and total duration of paroxysmal AF, total ectopic count, symptom assessments	Primary: There was not a significant difference in frequency of episodes of paroxysmal AF observed between the sotalol and atenolol groups (median difference, 0 min; 95% CI, 0 to 1; P=0.47). Secondary: There was not a significant difference in average duration of episodes of paroxysmal AF observed between the sotalol and atenolol groups (median difference, 0 min; 95% CI, 0 to 1 min; P=0.31) or in total duration of episodes of paroxysmal AF (median difference, 0 min; 95% CI, -1 to 2 min; P=0.51). There was not a significant difference in total ectopic count observed between the sotalol and atenolol groups (median difference, -123; 95% CI, -362 to 135; P=0.14) during either treatment period. There was not a significant difference in tolerance and symptom scores observed between the sotalol and atenolol groups (median difference, -5; 95% CI, -20 to 5; P=0.26)
Essential Tremor				
Calzetti et al.[55] (1981) Metoprolol 150 mg/dose vs propranolol 120 mg/dose vs placebo	DB, PC, RCT Patients 19 to 72 years with essential tremor and symptomatic for ≥1 year prior to the study	N=23 3 weeks	Primary: Tremor magnitude, heart rate, blood pressure Secondary: Not reported	Primary: Both metoprolol (47±9.7%) and propranolol (55±5.0%) significantly decreased tremor magnitude from baseline compared to placebo (22±7.3%; P<0.01 for both treatments compared to placebo), but there was not a significant difference observed between the metoprolol and propranolol groups. Both propranolol (0.073) and metoprolol (0.01) significantly diminished the normal increase in pulse rate on standing (P<0.01) and placebo had no effect on such pulse rate. There was not a significant difference observed between the metoprolol and propranolol groups. Both metoprolol and propranolol significantly reduced the SBP from baseline compared to placebo, in the supine and standing positions (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Yetimalar et al.[56] (2005) Propranolol 120 mg/day vs olanzapine 20 mg/day	DB, RCT, XO Patients with essential tremor and previous therapy with ≥1 medications for essential tremor without significant benefit, which was withdrawn ≥1 month before study drug was given	N=38 74 days	Primary: Tremor, global QOL Secondary: Not reported	Primary: After 30 days, both propranolol and olanzapine significantly reduced the all tremor evaluation measures (i.e., speaking, eating, dressing, writing working) compared to baseline (P=0.000), but at the end of the study, olanzapine significantly improved all tremor evaluation measures (P<0.05) except hygiene (P =0.08) as compared to propranolol. Both propranolol (63%) and olanzapine (87%) significantly improved global QOL from baseline, but olanzapine significantly improved the global QOL score compared to propranolol (4.5±0.7 vs 3.6±0.9; P=0.000). Secondary: Not reported
Gironell et al.[57] (1999) Propranolol 40 mg TID vs gabapentin 400 mg TID vs placebo	DB, PC, XO Patients with moderate to severe essential tremor that was chronic (≥5 years), persistent, and bilateral postural tremor with or without kinetic tremor involving hands or forearms, with no other neurological abnormalities or explanation for tremor	N=16 66 days	Primary: Tremor Clinical Rating Scale, accelerometric recordings, self-reported disability scale Secondary: Not reported	Primary: Both gabapentin and propranolol significantly reduced the clinical examination and motor task performance components of the Tremor Clinical Rating Scale compared to placebo (-3.10±1.10; P=0.01 and -4.50±1.10; P=0.001, respectively), and significant differences were not observed between the gabapentin and propranolol groups (1.40±1.16; P=0.23). Both gabapentin and propranolol significantly reduced the activities of daily living component of the Tremor Clinical Rating Scale compared to placebo (-3.03±1.46; P<0.05 and -4.95±1.46; P=0.002, respectively), and significant differences were not observed between the gabapentin and propranolol groups (1.92±1.46; P=0.20). Both gabapentin and propranolol significantly reduced the patient's subjective assessment of the Tremor Clinical Rating Scale compared to placebo (1.37±0.46; P=0.006 and 1.44±0.46; P=0.004, respectively). Significant differences were not observed between the gabapentin and the propranolol groups (-0.07±0.46; P=0.89). Both gabapentin and propranolol significantly reduced the absolute power of the dominant frequency peak of accelerometry compared to placebo

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				(-2352.0±1153.3; P=0.05 and -2282.14±1116.58; P=0.05, respectively), but significant differences were not observed between the gabapentin and the propranolol groups (-70.39±1165.22; P=0.95. Gabapentin significantly reduced the self-reported disability scale score more than placebo (-6.04±2.75; P=0.04) and propranolol did not (-4.48±2.75; P=0.11), but there were no significant differences between the gabapentin and propranolol groups (-1.55±2.75; P=0.58). Secondary: Not reported
Heart Failure				
CIBIS Investigators and Committees[58] (1994) CIBIS Bisoprolol 1.25 to 5 mg QD vs placebo All patient received standard therapy (diuretic and vasodilator)	DB, MC, PC, PG, RCT Patients 18 to 75 years with NYHA functional class III or IV due to idiopathic dilated cardiomyopathy, ischemia, HTN or valvular heart disease, a LVEF of <40%, and background therapy with a diuretic and a vasodilator	N=641 1.9 years	Primary: Total mortality Secondary: Tolerability, analysis critical events	Primary: There was no statistical significance between bisoprolol and placebo in total mortality (53 vs 67; RR, 0.80; 95% CI, 0.56 to 1.15; P=0.22). Secondary: Bisoprolol was well tolerated with no between group difference in premature treatment withdrawals (82 on placebo, 75 on bisoprolol; not significant). Significantly fewer patients in the bisoprolol group required hospitalization for cardiac decompensation (90 in placebo versus 61 in bisoprolol; P<0.01), and more patients improved by at least one NYHA functional class (48 on placebo versus 68 on bisoprolol; P=0.04) by the end of follow-up period.
CIBIS-II Investigators and Committees[59] (1999) CIBIS-II Bisoprolol 1.25 to 10 mg QD added	DB, MC, PC, RCT Symptomatic patients 18 to 80 years in NYHA class III or IV, with LVEF of 35% or less receiving	N=2,647 1.3 years	Primary: All-cause mortality Secondary: All-cause hospital admissions, cardiovascular mortality,	Primary: CIBIS-II was stopped early, after the second interim analysis, because bisoprolol showed a significant mortality benefit. All-cause mortality was significantly lower with bisoprolol than on placebo (156 [11.8%] vs 228 [17.3%] deaths, respectively; HR, 0.66; 95% CI, 0.54 to 0.81; P<0.0001). Significantly fewer sudden deaths among patients on bisoprolol than in those on placebo (48 [3.6%] vs 83 [6.3%] deaths, respectively; HR, 0.56;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
to usual therapy (diuretic and vasodilator) vs placebo	standard therapy with diuretics and ACE inhibitor or other vasodilator		cardiovascular mortality and cardiovascular hospital admissions (composite endpoint), permanent premature treatment withdrawals	95% CI, 0.39 to 0.80; P=0.0011). Secondary: All-cause hospital admissions was significantly lower with bisoprolol than on placebo (440 [33%] vs 513 [39%] patients, respectively; HR, 0.80; 95% CI, 0.71 to 0.91; P=0.0006). All-cardiovascular deaths was significantly lower with bisoprolol than on placebo (119 [9%] vs 161 [12%] patients, respectively; HR, 0.71; 95% CI, 0.56 to 0.90; P=0.0049). Occurrence of composite endpoints of all cardiovascular deaths and cardiovascular admissions was significantly lower with bisoprolol than on placebo (388 [29%] vs 463 [35%] patients, respectively; HR, 0.79; 95% CI, 0.69 to 0.90; P=0.0004). Occurrence of treatment withdrawals was not statistically different between bisoprolol and the placebo group (194 [15%] vs 192 [15%] patients, respectively; HR, 1.00; 95% CI, 0.82 to 1.22; P=0.98).
Contini et al.[60] (2013) CARNEBI Bisoprolol vs carvedilol vs nebivolol each at maximal clinically tolerated dose	RCT, XO Patients aged 18 to 80 years with diagnosis of either idiopathic or ischemic dilated cardiomyopathy, previous evidence of LVEF ≤ 40%, NYHA class I to III with stable clinical conditions and optimized drug regimen	N=61 Each patient performed a 2-month therapy with each β-blocker	Primary: Clinical conditions, quality of life, laboratory data, echocardiographic evaluation, spirometry, alveolar capillary membrane diffusion, chemoreceptor response, cardiopulmonary exercise test, and response to hypoxia during constant workload exercise	Primary: Clinical conditions, NYHA class, Minnesota questionnaire, renal function, hemoglobin concentration, brain natriuretic peptide, Echocardiographic data, and Doppler data were unaffected by the different β-blockers studied. Carbon monoxide diffusing capacity was lower on Carvedilol (18.3 ± 4.8* mL/min/mm Hg) compared to Nebivolol (19.9 ± 5.1) and Bisoprolol (20.0 ± 5.0) due to membrane diffusion 20% reduction (*= P< 0.0001). Constant workload exercise showed in hypoxia a faster VO_2 (oxygen uptake) kinetic and a lower ventilation with Carvedilol. Peripheral and central sensitivity to CO_2 was lower in Carvedilol while response to hypoxia was higher in Bisoprolol. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Not reported	
Willenheimer et al.[61] (2005) CIBIS-III Bisoprolol 1.25 to 10 mg QD vs enalapril 2.5 to 10 mg BID	BE, MC, OL, PG, RCT Patients ≥65 years with stable mild to moderate CHF (NYHA class II to III), LVEF of ≤35% ≥3 months prior to randomization, not on an ACE inhibitor, β-blocker or ARB therapy and no clinically relevant fluid retention of diuretic adjustment within the 7 days prior to randomization	N=1,010 1.22±0.42 years	Primary: Combined all-cause mortality or hospitalization Secondary: Combined end point at the end of the monotherapy phase and the individual components of the primary end point, cardiovascular death and cardiovascular hospitalization, permanent treatment cessation and the need for early introduction of the second drug as indicators of drug tolerability	Primary: There were 178 patients (35.2%) with a primary end point of combined all-cause mortality or all-cause hospitalization in the bisoprolol-first group, compared to 186 (36.8%) patients in the enalapril-first group (absolute difference, -1.6%; 95% CI, -7.6 to 4.4; HR, 0.94; 95% CI, 0.77 to 1.16; non-inferiority for bisoprolol-first vs enalapril-first treatment; P=0.019). Secondary: The combined endpoint at the end of the monotherapy phase occurred in 109 patients in the bisoprolol-first group compared to 108 patients in the enalapril-first group (HR, 1.02; 95% CI, 0.78 to 1.33; between-group difference P=0.90); 23 vs 32 patients died, respectively (HR, 0.72; 95% CI, 0.42 to 1.24; between-group difference P=0.24); and 99 vs 92 patients had been a hospitalization, respectively (HR, 1.08; 95% CI, 0.81 to 1.43; between-group difference P=0.59). There were 65 deaths in the bisoprolol-first group, as compared to 73 in the enalapril-first group (HR, 0.88; 95% CI, 0.63 to 1.22; between-group difference P=0.44). In the bisoprolol-first group, 151 patients were hospitalized, compared to 157 patients in the enalapril-first group (HR, 0.95; 95% CI, 0.76 to 1.19; between-group difference P=0.66). There was not a significant difference in cardiovascular death rate observed between the bisoprolol-first (55) and enalapril-first (56) treatment groups (HR, 0.97; 95% CI, 0.67 to 1.40; between-group difference P=0.86). During the monotherapy phase, 35 (6.9%) patients in the bisoprolol-first group permanently discontinued therapy, compared to 49 (9.7%) patients in the enalapril-first group. During the combined-therapy phase, 19 patients (4.2%) in the bisoprolol-first group permanently discontinued

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				bisoprolol therapy and 47 (10.4%) discontinued enalapril therapy. In the enalapril-first group, 24 patients (5.5%) permanently discontinued bisoprolol and 16 (3.7%) discontinued enalapril. There was not a statistical significant difference observed in the early introduction of the second drug between the bisoprolol-first group (39 [7.7%] patients) compared to the enalapril-first group (37 [7.3%] patients; P=0.81).
Packer et al.[62] (2001) COPERNICUS Carvedilol 3.125 to 25 mg BID vs placebo	DB, MC, PC, RCT Patients with severe chronic heart failure as a result of ischemic or nonischemic cardiomyopathy, dyspnea or fatigue at rest or on minimal exertion for ≥2 months and a LVEF <25% despite appropriate conventional therapy with diuretics, and an ACE inhibitor, or ARB	N=2,280 10.4 months	Primary: Total mortality Secondary: Combined risk of death or hospitalization for any reason, withdrawal rates	Primary: The study was stopped early due to statistical significance. The annual mortality in the placebo group was 19.7% (190) versus 12.8% (130 deaths) in the carvedilol group, a 35% reduction in mortality (95% CI, 19 to 48%; P<0.00013). Secondary: Carvedilol reduced the combined risk of death or hospitalization for any reason by 24% compared to placebo (425 vs 507 patients; 95% CI, 13 to 33%; P<0.001) Withdrawal rates were significantly higher in the placebo group compared to the carvedilol group (18.5 vs 14.8; P=0.02).
Packer et al.[63] (2002) COPERNICUS Carvedilol 3.125 mg BID, titrated up to 25 mg BID vs	DB, PC, RCT Patients with dyspnea or fatigue at rest or on minimal exertion for ≥2 months and a LVEF <25% as a result of an	N=2,289 10.4 months	Primary: All-cause mortality Secondary: Combined risk of death or hospitalization for any reason, combined risk of	Primary: The annual mortality rate with placebo was 19.7% per patient year of follow up, which was reduced to 12.8% by treatment with carvedilol, corresponding to a 35% reduction in the risk of death (P=0.00013). Secondary: Carvedilol reduced the risk of death or any hospitalization by 24% (P=0.00004).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	ischemic or nonischemic cardiomyopathy, being treated with a diuretic and either an ACE inhibitor or ARB		death or hospitalization for any cardiovascular reason, combined risk of death or hospitalization for heart failure, patient global assessment	Carvedilol reduced the combined risk of death or hospitalization for cardiovascular reason by 27% (P=0.0002) and the combined risk of death or hospitalization for heart failure by 31% (P=0.000004). Patients receiving carvedilol spent 27% fewer days in the hospital for any reason (P=0.005) and 40% fewer days in the hospital for heart failure (P<0.0001). More patients receiving carvedilol felt improved and fewer patients felt worse compared to patients receiving placebo after six months of maintenance therapy (P=0.0009). Patients receiving carvedilol were less likely to experience a serious adverse event (P=0.002), especially worsening heart failure, sudden death, cardiogenic shock or ventricular tachycardia.
Packer et al.[64] (1996) Carvedilol 3.125 mg BID, titrated up to 50 mg BID vs placebo	DB, PC, RCT Patients with symptoms of heart failure for ≥3 months and an ejection fraction ≤35%, despite ≥2 months of treatment with diuretics and an ACE inhibitor (if tolerated)	N=1,094 6 to 12 months	Primary: All-cause mortality, cardiovascular morbidity Secondary: Not reported	Primary: Thirty one (7.8%) patients receiving placebo died compared to 22 (3.2%) deaths in patients receiving carvedilol; this difference represents a 65% decrease in the risk of death (95% CI, 39 to 80; P<0.001). Treatment with carvedilol was associated with a large decrease in the risk of dying of progressive heart failure and in the risk of sudden death. Ninety eight (14.1%) patients receiving carvedilol and 78 patients (19.6%) receiving placebo had at least one hospitalization for cardiovascular causes; this difference represents a 27% reduction in the risk of hospitalization (95% CI, 3 to 45; P=0.036). Secondary: Not reported
Dargie et al.[65] (2001) CAPRICORN Carvedilol 6.25 to 25 mg BID mg vs	DB, MC, PC, RCT Patients 18 years and older with a stable MI occurring 3 to 21 days prior to randomization, LVEF ≤40% and	N=1,959 1.3 years	Primary: All-cause mortality, all-cause mortality or cardiovascular hospital admissions	Primary: There was not a significant difference observed between the carvedilol and placebo groups in the combined endpoint of all-cause mortality and hospital admissions due to cardiovascular events (340 [35%] vs 367 [37%], respectively; HR, 0.92; 95% CI, 0.80 to 1.07; P=0.296). All-cause mortality alone was statistically better in the carvedilol group than the placebo group (116 [12%] vs 151 [15%], respectively; HR, 0.77;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	ACE inhibitor therapy for ≥48 hours		Secondary: Sudden death, hospital admission for heart failure, recurrent nonfatal MI, all-cause mortality or recurrent nonfatal MI	95% CI, 0.60 to 0.98; P=0.031). Secondary: There was not a significant difference observed between the carvedilol and placebo groups in sudden death (51 [5%] vs 69 [7%], respectively; HR, 0.74; 95% CI, 0.51 to 1.06; P=0.098) or in hospital admissions for heart failure (118 [12%] vs 138 [14%], respectively; HR, 0.86; 95% CI, 0.67 to 1.09; P=0.215). The carvedilol group, compared to placebo, experienced significantly lower rates of nonfatal MIs (34 [3%] vs 57 [6%], respectively; HR, 0.59; 95% CI, 0.39 to 0.90; P=0.014) and all-cause mortality or recurrent nonfatal MI (139 [14%] vs 192 [20%], respectively; HR, 0.71; 95% CI, 0.57 to 0.89; P=0.002).
Krum et al.[66] (abstract) (1995) Carvedilol 25 mg BID vs placebo	DB, PC, RCT Patients with severe chronic HF receiving digitalis, diuretics and an ACE inhibitor (if tolerated)	N=56 14 weeks	Primary: Cardiac performance; symptom score; combined risk of death, worsening heart failure, and life-threatening ventricular tachycardia Secondary: Not reported	Primary: Compared to placebo, carvedilol improved cardiac performance, as reflected by an increase of LVEF (P=0.005) and stroke volume index (P=0.010), and a decrease in pulmonary wedge pressure (P=0.003), mean right atrial pressure (P=0.002) and systemic vascular resistance (P=0.017). Compared to placebo, carvedilol improved symptom scores (P=0.002), functional class (P=0.013) and submaximal exercise tolerance (P=0.006). The combined risk of death, worsening heart failure and life-threatening ventricular tachyarrhythmia was lower with carvedilol compared to placebo (P=0.028). Carvedilol was associated with more dizziness and advanced heart block. Secondary: Not reported
Bristow et al.[67] (1996) Carvedilol 6.25 mg BID	DB, MC, PC, RCT Symptomatic (≥3 months) patients, 18 to 85 years with stable heart failure	N=345 6 months	Primary: Submaximal exercise improvement Secondary:	Primary: There were no differences on submaximal exercise with any dose compared to placebo. Walk distances between in each group ranged between 300 to 400 m in both the 6-minute and 9-minute walk tests; P=0.50 and P=0.27, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs carvedilol 12.5 mg BID vs carvedilol 25 mg BID vs placebo All patients remained on their standard medications.	from ischemic or nonischemic dilated cardiomyopathy, an LVEF of ≤35%, a 6-minute walk test between 150 to 425 m and on stable doses of diuretics and ACE inhibitors for 2 weeks before baseline testing		Minnesota questionnaire, changes in NYHA functional class, changes in LVEF, hospitalization, changes in signs and symptoms of heart failure, occurrence of adverse clinical experiences, survival	Secondary: There were no significant changes in the overall Minnesota Questionnaire scores incorporating both physical and emotional dimensions (changes from baseline in the placebo and low-, medium-, and high-dose carvedilol groups of -7.3, -7.9, -7.3, and -6.6, respectively; P=0.512 in difference from placebo). There were no significant improvements in NYHA functional classes in the carvedilol groups compared to placebo (actual values not reported; P=0.64). Carvedilol treatment resulted in a dose-related significant improvement in LVEF; carvedilol 6.25 mg (~5 ejection fraction units; P<0.005), 12.5 mg (~6 ejection fraction units; P<0.005) and 25 mg (~7.5 ejection fraction units; P<0.0001) compared to placebo (2 ejection fraction unit improvement). The mean number of hospitalizations per patient were significantly reduced in each of the carvedilol groups (~0.1 hospitalizations) compared to placebo (~0.35; P<0.01). Bradycardia was significantly higher in the carvedilol 12.5 mg group (10 [11%]) and the 25 mg group (10 [11%]) compared to placebo (1 [1%]; P<0.05). Also, dizziness was significantly higher in the carvedilol 25 mg group (34 [38%]) compared to the placebo group (19 [23%]; P<0.05). The clinical significance of these advents was not mentioned. There was a dose-related, statistically significant reduction in mortality in the carvedilol-treated groups, with respective mortality rates of 6.0% for the carvedilol 6.25 mg group (RR, 0.356; 95% CI, 0.127 to 0.998; P<0.05), 6.7% for the 12.5 mg group (HR, 0.416; 95% CI, 0.158 to 1.097; P=0.07), and 1.1% in the 25 mg group (HR, 0.067; 95% CI, 0.009 to 0.512; P<0.001) compared to 15.5% mortality in the placebo group. Combining all three carvedilol arms of the study compared to the placebo arm showed statistical significance in all-cause mortality, risk reduced by 73% (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fröhlich et al.[68] (2015) Carvedilol with a median dose of 38 mg/day (75% of target dose) vs metoprolol succinate with a median dose of 103 mg/day (53% of target dose)	Cohort, PRO Patients with stable systolic chronic heart failure who were using either carvedilol or metoprolol succinate	N=4,016 Mean follow-up of 52.8±33.6 months	Primary: Mortality Secondary: Not reported	Primary: In the complete sample, 304 (27.2%) patients died in the carvedilol group and 1,066 (36.8%) in the metoprolol group. In a univariable analysis of the general sample, metoprolol therapy was associated with higher mortality compared with carvedilol therapy (HR, 1.49; 95% CI, 1.31 to 1.69; P<0.001). This difference was not seen after multivariable adjustment (HR, 0.93; 95% CI, 0.57 to 1.50; P=0.75) and adjustment for propensity score and dose equivalents (HR, 1.06; 95% CI, 0.94 to 1.20; P=0.36) or in the propensity and dose equivalent-matched sample (HR, 1.00; 95% CI, 0.82 to 1.23; P=0.99). These results were essentially unchanged for all prespecified subgroups. Secondary: Not reported
Poole-Wilson et al.[69] (2003) COMET Carvedilol 25 mg BID vs metoprolol 50 mg BID	DB, MC, PG, RCT Patients with NYHA class II to IV heart failure, admission for a cardiovascular reason in the previous 2 years, an LVEF of <35%, and were stable and optimized with diuretics for ≥2 weeks and ACE inhibitor for ≥4 weeks unless not tolerated	N=3,029 58 months	Primary: All-cause mortality, composite endpoint of mortality or all-cause admission Secondary: Not reported	Primary: All-cause mortality was significantly lower in the carvedilol group compared to the metoprolol group (512 [34%] vs 600 [40%], respectively; HR, 0.83; 95% CI, 0.74 to 0.93; P=0.0017). Cardiovascular deaths were significantly lower in the carvedilol group compared to the metoprolol group (438 [29%] vs 534 [35%], respectively; HR, 0.80; 95% CI, 0.70 to 0.90; P=0.0004). There was not a significant difference in the composite endpoints of all-cause mortality or all-cause admission observed between the carvedilol and metoprolol groups (1,116 [74%] vs 1,160 [76%], respectively; HR, 0.94; 95% CI, 0.86 to 1.02; P=0.122). Secondary: Not reported
Packer et al.[70] (2001) Carvedilol 50 to 100 mg/day	MA (19 trials) Patients with NYHA class II or III and LVEF	N=2,779 8.3 months	Primary: Change in LVEF Secondary: Not reported	Primary: In the six placebo-controlled trials, metoprolol significantly increased the mean LVEF by 0.063±0.002 compared to the increase with placebo of 0.025±0.001 (difference of 0.038±0.005; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs metoprolol 50 to 150 mg/day or metoprolol ER 150 to 200 mg/day or placebo	dysfunction			In the nine placebo-controlled trials, carvedilol significantly increased the mean LVEF by 0.079±0.001 compared to the increase with placebo of 0.012±0.001 (difference of 0.065±0.005; P<0.0001). Comparing the two agents, carvedilol increased the LVEF significantly greater than metoprolol (difference of 0.026±0.007; P=0.0002). In the four direct comparator trials, carvedilol significantly increased the mean LVEF by 0.089±0.002 compared to the increase with metoprolol of 0.055±0.002 (difference of 0.029±0.011; P=0.009). Secondary: Not reported
Arumanayagam et al.[71] (2001) Carvedilol 25 mg BID vs metoprolol 50 mg BID	DB, RCT Symptomatic Chinese patients with CHF and LVEF of <45%	N=24 12 weeks	Primary: Plasma total antioxidant status, erythrocyte superoxide dismutase and glutathione peroxidase Secondary: Not reported	Primary: Neither carvedilol nor metoprolol significantly reduced total antioxidant status activities after 12 weeks of therapy (1.65±0.06 to 1.68±0.09 and 1.44±0.05 to 1.51±0.06 mmol/L, respectively). Carvedilol significantly reduced erythrocyte superoxide dismutase activity after 12 weeks of therapy, (986±46 to 871±22 U/g Hb; P <0.001), but metoprolol did not (790±43 to 836±46 U/g Hb). Carvedilol significantly reduced glutathione peroxidase activity after 12 weeks of therapy, (145±7 to 132±9 U/g Hb; P <0.05), but metoprolol did not (143±8 to 138±9 U/g Hb). Secondary: Not reported
Sanderson et al.[72] (1999) Carvedilol 25 mg BID vs metoprolol 50 mg BID	DB, PG, RCT Symptomatic patients with CHF, LVEF of <45%, and on standard therapy (diuretics, digoxin and ACE inhibitor)	N=51 12 weeks	Primary: Symptom score (QOL questionnaire and NYHA class), exercise tolerance time, LVEF Secondary: Not reported	Primary: A significant improvement in symptom scores from baseline were experienced in both the carvedilol (17.2±3 to 8.1±2; P<0.001) and metoprolol (13.1±1.8 to 4.8±1.4; P<0.001) groups, but there was not a significant difference between the agents. A significant improvement in NYHA class from baseline were experienced in both the carvedilol (2.6±0.11 to 2.2±0.12; P<0.001) and metoprolol (2.7±0.09 to 2.1±0.09; P<0.001) groups, but there was not a significant difference between the agents.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
All patients continued on their standard therapy.				A significant improvement in exercise tolerance time from baseline were experienced in both the carvedilol (1122±51 to1194±63; P<0.05) and metoprolol (1164±46 to 1263±52; P<0.01) groups, but there was not a significant difference between the agents. A significant improvement in LVEF from baseline were experienced in both the carvedilol (26±1.8 to 35±2.6; P<0.001) and metoprolol (25±1.8 to 31±2.5; P<0.001) groups, but there was not a significant difference between the agents. Secondary: Not reported
Lechat et al.[73] (1998) β-blockers (bisoprolol, bucindolol, carvedilol, metoprolol, and nebivolol) vs placebo	MA (18 trials) Patients with NYHA class I to IV chronic heart failure	N=3,023 1.5 to 15 months	Primary: All-cause mortality, hospitalizations due to heart failure, combination of all-cause mortality and hospitalizations for worsened heart failure, changes in functional status, changes in LVEF Secondary: Not reported	Primary: All endpoints showed a significant effect for β-blockers (P<0.05). β-blockers demonstrated a 32% reduction in risk of death compared to placebo (130 vs 156 deaths; 95% CI, 12% to 47%; P=0.003). β-blockers demonstrated a 41% reduction in hospitalizations due to heart failure compared to placebo (166 vs 223 hospitalizations; 95% CI, 26% to 52%; P<0.001). β-blockers demonstrated a 37% reduction in the combination of mortality and morbidity compared to placebo (239 vs 293; 95% CI, 24% to 49%; P<0.001). β-blockers demonstrated a 32% increase in the likelihood of improvement in NYHA class (95% CI, 1% to 74%; P=0.04) and a 30% decrease in the likelihood of worsening NYHA (95% CI, 4% to 50%; P=0.03) compared to placebo β-blockers demonstrated a 29% increase in ejection fraction compared to placebo (0.23±0.04 vs 0.31±0.04; P<10–9). β-adrenergic agents did not differ in respect to any outcome measure except that reduction in mortality risk. Beta-selective agents were less

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				robust than the nonselective agents (P=0.049). Secondary: Not reported
Brophy et al.[74] (2001) β-blockers (bisoprolol, bucindolol, carvedilol, metoprolol and nebivolol) vs placebo	MA (22 trials) Patients with CHF of various etiologies	N=10,135 3 to 23 months	Primary: Overall mortality, hospitalizations for CHF Secondary: Not reported	Primary: β-blockers significantly reduced mortality compared to placebo (444 vs 624; OR, 0.65; 95% CI, 0.53 to 0.80). β-blockers significantly reduced hospitalizations due to CHF compared to placebo (540 vs 754; RR, 0.64; 95% CI, 0.53 to 0.79). The probability that β-blocker therapy reduced total mortality and hospitalizations for congestive heart failure was almost 100%. The best estimates of these advantages are 3.8 lives saved and four fewer hospitalizations per 100 patients treated in the first year after therapy. The probability that these benefits are clinically significant (>2 lives saved or >2 fewer hospitalizations per 100 patients treated) is 99%.
Whorlow et al.[75] (2000) β-blockers (bisoprolol, bucindolol, carvedilol metoprolol, nebivolol) vs placebo	MA (18 trials) Patients with NYHA class IV heart failure currently taking background therapy (ACE inhibitors and diuretics with or without digoxin)	N=8,119 3 to 21 months	Primary: Mortality in NYHA class IV patients Secondary: Not reported	Primary: β-blockers demonstrated a 29% reduction in mortality compared to placebo in patients with NYHA class IV (RR, 0.71; 95% CI, 0.52 to 0.96). The 29% risk reduction is similar to risk reduction seen with β-adrenergic blockers in other NYHA classes. β-blockers demonstrated a 32% reduction in mortality compared to placebo in patients with NYHA class I to IV (HR, 0.68; 95% CI, 0.61 to 0.77). Secondary: Not reported
Bouzamondo et al.[76] (2003) β-blockers (bisoprolol, bucindolol,	MA Randomized controlled evaluating patients with heart failure depending on	N=not specified Duration varied	Primary: Overall mortality, hospitalized for worsening heart failure Secondary:	Primary: β-blockers reduced overall mortality by 22% compared to placebo (95% CI, 16% to 28%). β-blockers reduced hospitalizations due to worsening heart failure by 24% compared to placebo (95% CI, 20% to 29%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
carvedilol, and metoprolol) vs placebo	NYHA class		Not reported	Benefits were similar for bisoprolol, metoprolol, and carvedilol regardless of NYHA class. Secondary: Not reported
Jabbour et al.[77] (2010) β-blockers (bisoprolol, carvedilol, metoprolol)	OL, XO Patients with NYHA class I to III heart failure with a subgroup of patients with coexisting COPD	N=51 16 weeks	Primary: Post-bronchodilator FEV_1 Secondary: Not reported	Primary: FEV_1 was significantly higher in patients receiving bisoprolol vs carvedilol, both in those with coexisting COPD (P<0.01) and without (P=0.02). There was a significant difference between all patients receiving carvedilol versus those receiving metoprolol (P=0.04), however, when compared for coexisting COPD, there was no difference in FEV_1. There was no significant difference for all patients, those with COPD, or those with CHF only when metoprolol and bisoprolol were compared.
MERIT-HF Study Group[78] (1999) MERIT-HF Metoprolol CR/XL 12.5 mg up to 200 mg QD vs placebo	DB, MC, PC, RCT Symptomatic patients 40 to 80 years in NYHA class II to IV, with LVEF of 40% or less stabilized on standard therapy (diuretic and vasodilator)	N=3,991 1 year	Primary: All-cause mortality, all-cause mortality in combination with all-cause admission to hospital (time to first event) Secondary: Not reported	Primary: Study was stopped early on the recommendation of the independent safety committee. All-cause mortality was significantly lower in the metoprolol CR/XL group than in the placebo group (145 [7.2%] vs 217 [11.0 %] deaths, RR, 0.66; 95% CI, 0.53 to 0.81; P=0.00009). There were significantly fewer sudden deaths in the metoprolol CR/XL group than in the placebo group (79 vs 132; RR, 0.59; 95% CI, 0.45 to 0.78; P=0.0002) and deaths from worsening heart failure (30 vs 58; RR, 0.51; 95% CI, 0.33 to 0.79; P=0.0023). Study drug was permanently stopped early in 13.9% of the patients in the metoprolol CR/XL group and in 15.3% of patients in the placebo group (RR, 0.90; 95% CI, 0.77 to 1.06). Secondary: Not reported
Goldstein et al.[79] (2001) MERIT-HF	Sub group analysis of MERIT-HF	N=795 1 year	Primary: All-cause mortality,	Primary: There were 45 deaths (11.7% per patient year of follow-up) with metoprolol and 72 deaths (19.1%) with placebo. Metoprolol decreased

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Metoprolol CR/XL 12.5 mg, titrated up to 200 mg QD vs placebo	Patients with NYHA Class III to IV heart failure with LVEF <25%		composite of all-cause mortality and all-cause admission to hospital (time to first event) Secondary: Not reported	total mortality by 39%, sudden death by 45% and death due to worsening heart failure by 55%. Metoprolol also decreased the combined end points of all-cause mortality or all-cause hospitalization by 29%, all-cause mortality or hospitalization for worsening heart failure by 44% and cardiac death or nonfatal MI by 46%. Metoprolol reduced the total number of hospitalizations (all-cause) by 27% (0.709 vs 0.965 per patient year of follow up; P=0.0037). During the up titration phase of the trial, the cumulative numbers of patients hospitalized (all-cause) were: 17 vs 21 after two weeks, 28 vs 30 after four weeks, 39 vs 40 after six weeks, 46 vs 56 after eight weeks and 76 vs 102 after three months. The total number of hospitalizations for cardiovascular causes was reduced by 34% (0.475 vs 0.715 per patient year of follow up; P=0.0005) and for worsening heart failure by 45% (0.273 vs 0.497; P<0.0001). Improvement in NYHA functional class was recorded in 46.2 vs 36.7% of patients receiving metoprolol and placebo (P=0.0031). Secondary: Not reported
Waagstein et al.[80] (1993) MDC Metoprolol 5 mg BID, titrated up to 100 to 150 mg/day vs placebo	DB, MC, PC, PG, RCT Patients 16 to 75 years of age with symptomatic dilated cardiomyopathy, an ejection fraction <40% and being treated with diuretics, ACE inhibitors and nitrates	N=383 18 months	Primary: Combined all-cause mortality and clinical deterioration to a point at which cardiac transplantation would normally be offered as a treatment option Secondary:	Primary: Thirty eight patients receiving placebo reached the primary endpoint compared to 25 patients receiving metoprolol, which corresponded to a risk reduction of 34% (95% CI, -6 to 62; P=0.058). With regard to the individual endpoints, 21 patients met the non-fatal endpoint of need for heart transplantation; two and 19 patients receiving metoprolol and placebo (P=0.0001). During the 12 or 18 months of follow up, all-cause mortality were 23 and 21 patients receiving metoprolol and placebo (P value not reported). Secondary: There was a significantly greater increase in ejection fraction with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Cardiac function, exercise capacity, QOL, hospital admission or emergency visits for HF treatment	metoprolol compared to placebo by six and 12 months (P value not reported). QOL improved significantly more with metoprolol compared to placebo (P=0.01). With metoprolol, exercise capacity was significantly greater at six and 12 months compared to baseline (P=0.0006 and P=0.0007). With placebo there was a significant improvement from baseline at six months (P=0.007), but not at 12 months (P=0.46). The difference between the two treatments was significant only at 12 months (P=0.046). There was no difference between the treatments in the number of patients readmitted to the hospital (28 vs 20%; P=0.12), but the number of readmissions for all patients in the group was significantly lower with metoprolol (83 vs 51) as was the mean number of readmissions per patient (0.47 vs 0.28; P<0.04).
Di Lenarda et al.[81] (1999) Metoprolol 142±44 mg QD vs carvedilol 12.5 mg to 50 mg BID	OL, PG, RCT Symptomatic (>12 months) patients with stable dilated cardiomyopathy, LVEF of ≤40% and who poorly responded to chronic treatment with metoprolol plus conventional therapy (metoprolol plus ACE inhibitor, digitalis, diuretics), persistent moderate-to-severe left ventricular dysfunction and reduced exercise	N=30 12 months	Primary: Improvement in left ventricular function and remodeling Secondary: Effects on symptoms, QOL, exercise tolerance, ventricular arrhythmias	Primary: LVEF significantly improved in the carvedilol group (7±3%) compared to the metoprolol group (-1±2%; P=0.045). LV end-systolic volume was significantly improved in the carvedilol group (-7±5) compared to the metoprolol group (6±4 mL/m^2; P=0.047). There was not a significant difference in LV end-diastolic volume observed between the carvedilol (-8±7) and the metoprolol group (7±6 mL/m^2; P=0.053). Secondary: There was not a significant difference observed in the NYHA class, the Heart Failure Score, the Minnesota “Living With Heart Failure” Questionnaire and submaximal exercise tolerance did not significantly change between the carvedilol and metoprolol groups. Carvedilol, compared to metoprolol, demonstrated a positive effect on ventricular ectopic beats (-12±9 vs 62±50 n/h; P=0.05) and couplets (-0.5±0.4 vs 1.5±0.6 n/h; P=0.048), but not a significant effect on episodes of nonsustained ventricular tachycardia (-0.02±0.03 vs 0.03±0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	tolerance			
Maack et al.[82] (2001) Metoprolol 12.5 to 100 mg BID vs carvedilol 3.125 to 25 mg BID	OL, XO Patients with stable NYHA class I to III heart failure due to ischemic or idiopathic dilated cardiomyopathy and an LVEF of <35%	N=80 6 months	Primary: Change in LVEF and change in baseline hemodynamic properties (left ventricular end diastolic, end systolic volume, NYHA class) Secondary: Not reported	Primary: After six months of treatment, LVEF improved in the carvedilol group (32±3 to 36±4%; P<0.05 vs baseline) and in the metoprolol group (27±4 to 30±5%; P<0.05 vs baseline). There was not a statistical difference between the agents. There were no differences between the groups in left ventricular end diastolic, end systolic volume, NYHA functional class or any other hemodynamic parameters at rest. Secondary: Not reported
Metra et al.[83] (2000) Metoprolol 5 to 100 mg BID vs carvedilol 3.125 to 50 mg BID All patients continued on their usual treatment for heart failure.	DB, PRO, RCT Symptomatic (≥6 months) patients with CHF caused by ischemic or nonischemic cardiomyopathy, NYHA class II to IV, LVEF ≤35% and a peak oxygen uptake ≤25 mL/kg-1/min-1 and on constant background therapy (furosemide and ACE inhibitor or ARB) for 1 week prior to the study	N=150 15 months	Primary: Change in LVEF Secondary: Hemodynamic variables at rest and peak exercise, maximal and submaximal exercise tolerance, QOL, NYHA functional class, frequency of death and urgent transplantation	Primary: Both agents significantly increased LVEF from baseline (P<0.001 for both), but carvedilol increased LVEF significantly greater at the than metoprolol (10.9±11 vs 7.2±7.7%; P=0.038). Secondary: At the end of the study, both agents carvedilol and metoprolol increased stroke volume and stroke work indexes and decreased mean pulmonary artery pressure, pulmonary wedge pressure, and heart rate from baseline (all P<0.05 from baseline). However, the increase in stroke volume and stroke work indexes during exercise and the decreases in mean pulmonary artery pressure and pulmonary wedge pressure at both rest and exercise were greater with carvedilol than with metoprolol (all P<0.05). Carvedilol increased rest and exercise cardiac index from baseline (both P<0.05). Heart rate declined with both drugs at rest and exercise, but the decrease in exercise heart rate with carvedilol was greater than with metoprolol (P<0.05 for the difference between the groups). Both metoprolol and carvedilol significantly improved NYHA class, 6-minute walk distance, and QOL scores from baseline (all P<0.05), and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				there were no differences between the two treatments. Overall, 21 patients in the metoprolol group and 17 patients in the carvedilol group died or underwent urgent transplantation.
Hypertension				
Reim et al.[84] (1985) Acebutolol 400 mg QD vs propranolol 160 mg QD	DB, MC, XO Patients 18 to 70 years with essential HTN and blood pressure of >150/90 mm Hg	N=18 14 weeks	Primary: Blood pressure and heart rate during ergometer exercise test Secondary: Not reported	Primary: There was not a significant difference observed between the acebutolol and propranolol groups in decreases in blood pressure (systolic and diastolic) and heart rate at rest (P=0.123, P=0.230 and P=0.210, respectively). At the ergometer 25 watt load, heart rate and DBP were not significantly different between acebutolol and propranolol (P=0.087 and P=0.068, respectively), but SBP was significantly lower in the acebutolol group (P=0.042) At the higher ergometer loads of 50 and 75 watts, acebutolol had a significantly lower increase in SBP and heart rate compared to propranolol during exercise (50 watts: P=0.004 and P=0.012, respectively; 75 watts: P=0.005 and P=0.001, respectively), but there was not a significant difference observed between the groups in DBP in the 50 and 75 watt loads (P=0.057 and P=0.058, respectively). At the highest ergometer load of 100 watts, acebutolol significantly reduced systolic and DBPs and heart rate compared to propranolol (P=0.003, P=0.001, and P=0.001, respectively). Secondary: Not reported
Fogari et al.[85] (1984) <u>Weeks 1 to 4:</u> Atenolol 50 mg QD vs	RCT, SB Patients 61 to 80 years inadequately controlled (SBP >170 mm Hg and/or DBP >100 mm Hg) on antihypertensive	N=38 6 months	Primary: Changes in blood pressure Secondary: Not reported	Primary: After the first four weeks, atenolol (from 177.5 to 161.1 mm Hg) significantly reduced blood pressure compared to baseline, but chlorthalidone did not (from 176.6 to 179.1 mm Hg). The combination atenolol-chlorthalidone therapy significantly reduced mean standing SBP and DBP, supine SBP and DBP, supine and standing heart rate, compared to previous therapies (P<0.001 for all comparisons).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
chlorthalidone 12.5 mg QD <u>Weeks 5 to study end:</u> atenolol and chlorthalidone 50-12.5 mg QD (fixed-dose combination product)	medications			The combination atenolol-chlorthalidone therapy significantly reduced mean standing SBP and DBP, supine SBP and DBP, supine and standing heart rate, compared to atenolol and chlorthalidone monotherapy (P<0.001 or P<0.01 for all comparisons). Mean blood pressure reduction obtained by the atenolol and chlorthalidone combination product was 30/15 mm Hg in the standing position (P<0.001). Serum potassium increased with atenolol-chlorthalidone (4.45 mEq/L) compared to chlorthalidone alone (4.01 mEq/L; P<0.001). Secondary: Not reported
Leonetti et al.[86] (1986) Atenolol 50 mg QD vs atenolol 100 mg QD vs chlorthalidone 12.5 mg QD vs atenolol and chlorthalidone 50-12.5 mg QD (fixed-dose	DB, RCT Patients 24 to 68 years with mild to moderate HTN (WHO stage I or II), with supine DBP ≥95 mm Hg at the end of the 4-week washout period	N=28 16 weeks	Primary: Changes in blood pressure Secondary: Not reported	Primary: Mean supine blood pressure was significantly reduced in all treatment groups compared to placebo: 153±18/93±9 mm Hg for atenolol 50 mg patients, 155±22/91±8 mm Hg for atenolol 100 mg patients, 148±17/93±11 mm Hg for chlorthalidone 12.5 mg patients, and 144±16/89±6 mm Hg for the atenolol-chlorthalidone combination patients. All of the changes in blood pressure were significant (P<0.01) versus placebo. Supine SBP was lower with atenolol-chlorthalidone than with the atenolol 100 mg alone (P<0.05). Upright SBP was lower with atenolol-chlorthalidone than with atenolol 50 mg alone (P<0.05) and atenolol 100 mg alone (P<0.05). Mean supine heart rate was 77±7 bpm after placebo which decreased to 69±10 bpm (P<0.01) after atenolol 50 mg, to 67±6 bpm (P<0.01) after atenolol 100 mg, to 77±10 bpm (P=not significant, was not reported) after chlorthalidone alone. Chlorthalidone alone demonstrated a significant reduction in serum potassium levels compared to placebo (3.88 vs 4.09 mEq/L; P<0.05) and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
combination product)				no change when the atenolol-chlorthalidone combination was compared to placebo (3.98 vs 4.09; P=not significant, value was not reported). Chlorthalidone alone and atenolol-chlorthalidone demonstrated a significant increase in serum uric acid levels compared to placebo (4.90±1.52 mg/dL, 5.07±1.33 mg/dL, respectively, vs 4.24±1.12 for placebo; P<0.05 for both). All treatments were well tolerated. Some adverse events reported included dyspnea, precordial discomfort and cold extremities. Incidence, severity and P values were not reported.
Nissinen et al.[87] (1980) Atenolol 100 mg QD plus chlorthalidone 25 mg in the morning vs atenolol and chlorthalidone 100-25 mg in the morning (fixed-dose combination product) vs placebo	DB, RCT Patients with newly diagnosed mild to moderate HTN (supine DBP 100 mm Hg on ≥3 occasions)	N=23 16 weeks	Primary: Changes in blood pressure and heart rate Secondary: Not reported	Primary: Each of the active drug combinations lowered standing, supine, and post-exercise blood pressure significantly compared to placebo at two and four weeks (P<0.001, P<0.01 and P<0.05). There was not a statistical difference between the active treatment regimens (P value not significant). Each of the active drug combinations lowered standing, supine, and post-exercise heart rate significantly compared to placebo at two and four weeks (P<0.001, P<0.01 and P<0.05). There was not a statistical difference between the active treatment regimens (P value not significant). Side effects did not differ between treatment groups and placebo in terms of frequency or severity. Reported side effects included dizziness, headache and tiredness. Secondary: Not reported
Johnson et al.[88] (2009) Atenolol 50 to 100 mg QD for 9 weeks, followed	RCT Patients 17 to 65 years of age mild to moderate essential HTN	N=368 15 to 18 weeks	Primary: Blood pressure lowering effect of drug initiation order: the addition of a β-blocker to a	Primary: When analyzed by order of initiation of the two drugs, the response to HCTZ and atenolol was greater overall than that seen for atenolol and HCTZ (P=0.0007 and P<0.0001). This study suggests that initiation of HCTZ followed by atenolol results in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
by atenolol 50 to 100 mg QD and HCTZ 12.5 to 25 mg QD for 9 weeks vs HCTZ 12.5 to 25 mg QD for 9 weeks, followed by HCTZ 12.5 to 25 mg QD and atenolol 50 to 100 mg QD for 9 weeks			thiazide versus the addition of a thiazide to a β-blocker Secondary: Not reported	greater blood pressure lowering as compared with initiation in the reverse order, with differences that are potentially clinically important. Secondary: Not reported
Dhakam et al.[89] (2008) Atenolol 50 mg QD vs nebivolol 5 mg QD vs placebo QD	DB, RCT, XO Never-treated subjects with isolated systolic HTN	N=16 17 weeks	Primary: Change in central blood pressure Secondary: Change in peripheral blood pressure, AIx, aPWV and N-terminal proBNP.	Primary: There was not a statistically significant difference observed in the change in aortic SBP between the nebivolol and atenolol groups (125±3 vs 127±3 mm Hg; P=0.4), but both agents were significantly better than placebo (131±2 mm Hg). There was not a statistically significant difference observed in the change in aortic DBP between the nebivolol and atenolol groups (75±2 vs 73±2 mm Hg; P=0.3), but both agents were better than placebo (82±2 mm Hg). Secondary: There was not a statistically significant difference observed in the change in brachial SBP between the nebivolol and atenolol groups (136±3 vs 137±3 mm Hg; P=0.4), but both agents were significantly better than placebo (149±3 mm Hg). There was not a statistically significant difference observed in the change in brachial DBP between the nebivolol and atenolol groups (75±2 vs 73±2 mm Hg; P=0.5), but both agents were better than placebo (82±2 mm Hg). There was a statistically significant reduction in AIx in the atenolol group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				compared to the nebivolol group (32±2 vs 28±2%; P=0.4), but both agents were significantly better than placebo (22±2%). There was not a statistically significant difference observed in the reduction of aPWV in the atenolol group compared to the nebivolol group (8.9±0.3 vs 9.1±0.3 m/s; P=0.2), but both agents were significantly better than placebo (10.0±0.4 m/s; P was not reported). There was not a statistically significant difference observed in the rise in N-terminal pro-BNP in the atenolol group compared to the nebivolol group (157 vs 138 pg/mL; P=0.6), but both agents were significantly better than placebo (75 mg/mL).
Fogari et al.[90] (1997) Atenolol 50 mg QD vs nebivolol 5 mg QD	DB, PG, RCT Patients 18 to 70 years of age with stable type 2 diabetes (HbA_{1c} ≤8% during previous 6 months with diet and/or oral therapy stable for ≥6 months), and mild to moderate HTN (DBP ≥95 and <116 mm Hg) at the end of the 4-week run-in period with placebo	N=30 6 months	Primary: Changes in blood pressure, heart rate, 24-hour urinary C-peptide excretion, HbA_{1c}, plasma glucose, lipid levels Secondary: Euglycemic hyperinsulinemic clamp test (body glucose utilization)	Primary: Both atenolol and nebivolol significantly reduced blood pressure and heart rate from baseline (P<0.001 for all measures), but there was not a significant difference between the treatment groups at weeks 0, 2, and 24 (P>0.05 for all measures). There no significant changes from baseline in mean 24-hour urinary C-peptide excretion, HbA_{1c}, plasma glucose, and lipid levels (P>0.05). There were also no significant differences observed between treatment groups in any of these measures (P>0.05). Secondary: There was not a significant decrease from baseline in mean values for whole body glucose utilization observed in neither the atenolol group nor the nebivolol group (mean decrease of 0.9 vs 2.6%, respectively; P>0.05) and the groups were significant from each other (P>0.05).
Dietz et al.[91] (2008) Atenolol 50 to 100 mg QD vs	DB, MC, RCT Patients ≥18 years of age with HTN (mean sitting DBP ≥95 and <110 mm Hg)	N=694 12 weeks	Primary: Changes in mean sitting SBP and mean sitting DBP, rates of blood pressure control (<140/90 mm Hg), pulse pressure and	Primary: Treatment with aliskiren and atenolol combination therapy led to a significantly greater reduction in mean sitting SBP by 17.3 mm Hg compared to aliskiren monotherapy (difference, -2.9 mm Hg; P=0.039) or atenolol monotherapy (difference, -3.0 mm Hg; P=0.034). There was no difference between mean sitting SBP reductions with aliskiren and atenolol monotherapy (difference, -0.1 mm Hg; P=0.954).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
aliskiren 150 to 300 mg QD vs aliskiren 150 to 300 mg and atenolol 50 to 100 mg QD			pulse rate, plasma renin concentration, plasma renin activity Secondary: Not reported	Treatment with aliskiren and atenolol combination therapy led to a significantly greater reduction in mean sitting DBP by 14.1 mm Hg compared to aliskiren monotherapy (difference, -2.9 mm Hg; P<0.001), but not atenolol monotherapy (difference, -0.5 mm Hg; P=0.545). Reductions in mean sitting DBP with atenolol were larger compared to those observed with aliskiren (difference, 2.4 mm Hg; P=0.003). Rates of blood pressure control were higher with aliskiren and atenolol combination therapy (51.3%) compared to aliskiren monotherapy (36.1%, P<0.001) or atenolol monotherapy (42.2%, P=0.009). There was no significant difference in blood pressure control rates between aliskiren and atenolol monotherapy (P=0.388). Mean pulse pressure was reduced by 3.0 mm Hg with aliskiren and atenolol combination therapy and aliskiren monotherapy. Atenolol monotherapy did not affect pulse pressure. Aliskiren monotherapy did not affect pulse rate. Significant mean reductions in pulse rate of >10 bpm were observed with atenolol monotherapy and the aliskiren and atenolol combination (P<0.001 vs aliskiren monotherapy for both). Aliskiren monotherapy increased plasma renin concentration by 241% and aliskiren/atenolol increased plasma renin concentration by 85% (P=0.010 vs aliskiren). Atenolol monotherapy decreased plasma renin concentration by 24% (P<0.001 vs aliskiren and aliskiren/atenolol). Aliskiren, atenolol and aliskiren/atenolol reduced plasma renin activity by 65, 52, and 61%, respectively. Secondary: Not reported
Wald et al.[92] (2008) Atenolol 25 mg QD vs	DB, DD, RCT, XO Patients ≥ 40 years enrolled in a HTN or anticoagulation clinic	N=47 16 weeks	Primary: Reduction in blood pressure Secondary: Not reported	Primary: The mean reductions in SBP in the atenolol alone, lisinopril alone and atenolol plus lisinopril groups were 16.1, 12.5 and 22.9 mm Hg, respectively. The mean reductions in DBP in the atenolol alone, lisinopril alone and atenolol plus lisinopril groups were 9.8, 6.8 and 13.9 mm Hg, respectively. The reductions with lisinopril plus atenolol group were significantly higher than either agent as monotherapy (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
lisinopril 5mg QD vs lisinopril 5 mg and atenolol 25 mg QD vs placebo				Secondary: Not reported
Pareek et al.[93] (2010) Atenolol 25 to 50 mg QD vs amlodipine 2.5 to 5 mg and atenolol 25 to 50 mg QD	AC, MC, OL, RCT Adults with either untreated or pretreated essential HTN	N=190 12 weeks	Primary: Change in SBP and DBP Secondary: Not reported	Primary: At the end of four weeks, the mean change in SBP (-30.0±10.4 vs -25.08±9.05; P=0.008) and DBP (-18.10±7.45 vs -14.78±7.48; P=0.021) was significantly greater in the low-dose combination therapy as compared to the low-dose monotherapy. At the end of 12 weeks, the mean SBP (127.82±8.90 vs 138.0±14.4; P=0.001) and mean DBP (81.73±8.78 vs 87.35±5.50; P=0.011) were significantly lower in the high-dose combination group as compared to the high-dose monotherapy group. Secondary: Not reported
Chapman et al.[94] (2007) ASCOT-BPLA Atenolol 50 to 100 mg titrated to target blood pressure <140/90 mm Hg (or <130/90 mm Hg in diabetic patients); bendro-flumethiazide* plus potassium	Subanalysis of ASCOT-BPLA evaluating effects of spironolactone on treatment-resistant HTN Patients 40 to 79 years of age with HTN and ≥3 cardiovascular risk factors, with SBP ≥160 mm Hg and/or DBP ≥100 mm Hg	N=1,411 1.3 years	Primary: Change in DBP and SBP, adverse effects Secondary: Not reported	Primary: Spironolactone-treated patients lead to a significant 21.9 mm Hg reduction in SBP among patients whose blood pressure was previously uncontrolled on at least three other antihypertensive drugs (95% CI, 20.8 to 23.0 mm Hg; P<0.001). Spironolactone-treated patients lead to a significant 9.5 mm Hg reduction in DBP among patients whose blood pressure was previously uncontrolled on at least three other antihypertensive drugs (95% CI, 9.0 to 10.1; P<0.001). Spironolactone-treated patients exhibited small but significant decreases in sodium, LDL-C and TC as well as increases in potassium, glucose, creatinine and HDL-C (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
1.25 to 2.5 mg plus doxazosin were added for additional blood pressure control; if blood pressure remained elevated on the 3 above drugs, spironolactone 25 mg was added to the regimen vs amlodipine 5 to 10 mg titrated to target blood pressure <140/90 mm Hg (or <130/90 mm Hg in diabetic patients); perindopril 4 to 8 mg and doxazosin were added for additional control; if blood pressure remained elevated on the 3 above drugs, spironolactone 25 mg was added to the regimen	(not on antihypertensive therapy) or SBP ≥140 mm Hg and/or DBP ≥90 mm Hg (on antihypertensive therapy)			The most common adverse effect reported in the trial was gynecomastia in men (P value not reported). Secondary: Not reported
Pepine et al.[95] (2006) INVEST	Post hoc analysis of INVEST Patients with	N=22,576 24 months	Primary: Risk for adverse outcome associated with baseline	Primary: Previous heart failure (adjusted HR, 1.96), as well as diabetes (HR, 1.77), increased age (HR, 1.63), United States residency (HR, 1.61), renal impairment (HR, 1.50), stroke/TIA (HR, 1.43), smoking (HR, 1.41), MI

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Atenolol (step 1), then add HCTZ if needed (step 2), then increase doses of both (step 3), then add trandolapril (step 4) (non-calcium antagonist strategy) vs verapamil SR (step 1), then add trandolapril if needed (step 2), then increase doses of both (step 3), then add HCTZ (step 4) (calcium antagonist strategy)	essential HTN		factors, follow-up blood pressure and drug treatments Secondary: Not reported	(HR, 1.34), PVD (HR, 1.27), and revascularization (HR, 1.15) predicted increased risk. Follow-up SBP <140 mm Hg (HR, 0.82) or DBP <90 mm Hg (HR, 0.70) and trandolapril with verapamil SR (HR, 0.78 and 0.79) were associated with reduced risk. Secondary: Not reported
Denardo et al.[96] (2015) INVEST Atenolol (step 1), then add HCTZ if needed (step 2), then increase doses of both (step 3), then add trandolapril (step 4) (non-calcium antagonist strategy)	Subgroup analysis of INVEST INVEST patients (patients with clinically stable hypertension and CAD) who underwent 24-hour ambulatory monitoring prior to randomization ("baseline") and after one year of	N=117 One year	Primary: BP, HR, pulse pressure Secondary: Not reported	Primary: Hourly SBP and DBP decreased after one year for both verapamil SR- and atenolol-based treatment strategies compared with baseline (P<0.0001). Atenolol also decreased hourly HR (P<0.0001). Both treatment strategies decreased SBP variability (weighted standard deviation: P=0.012 and 0.021, respectively). Compared with verapamil SR, atenolol also increased the prevalence of BP and HR nighttime dipping among prior non-dippers (BP: OR,3.37; 95% CI, 1.26 to 8.97; P=0.015; HR: OR, 4.06; 95% CI, 1.35 to 12.17; P=0.012) and blunted HR morning surge (2.8 vs 4.5 beats/min/hr; P=0.019). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs verapamil SR (step 1), then add trandolapril if needed (step 2), then increase doses of both (step 3), then add HCTZ (step 4) (calcium antagonist strategy)	treatment			
Hilleman et al.[97] (1999) Monotherapy (atenolol, HCTZ, captopril, enalapril, lisinopril, amlodipine, diltiazem, nifedipine, verapamil) vs amlodipine and benazepril (fixed-dose combination)	MA (82 trials) Patients with mild-to-moderate essential HTN	N=not reported ≥4 weeks	Primary: Absolute change in supine DBP from baseline Secondary: Percent of patients who achieved blood pressure control, safety	Primary: The mean absolute decrease in supine DBP ranged from 9.7 to 13.3 mm Hg with verapamil showing the greatest effect and captopril the least. When studies were weighted by sample size, amlodipine and benazepril, atenolol, lisinopril, and verapamil showed the greatest blood pressure effect. Secondary: The average percentage of patients defined as controlled after treatment varied from 53.5 to 79.0%, with amlodipine and benazepril (74.3%) and lisinopril (79.0%) showing the highest percentage control (P=0.096). The incidence of adverse events ranged from 12.1 to 41.8%, with lisinopril and verapamil showing the lowest incidences (12.1% and 14.1%, respectively) and nifedipine the highest incidence. Lisinopril demonstrated significantly less overall side effects compared to nifedipine (P=0.030). Nifedipine demonstrated a higher withdrawal rate due to side effects compared to atenolol, HCTZ, enalapril, amlodipine, and diltiazem (P=0.002). Although amlodipine and benazepril had the lowest rate of withdrawals due to adverse events, lack of significant change was due to the low number of cohorts available for analysis.
Davidov et al.[98] (1988)	DB, MC, RCT	N=141	Primary: Change in blood	Primary: Both betaxolol and propranolol significantly reduced SBP from baseline

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Betaxolol 10 to 40 mg QD vs propranolol 40 to 160 mg BID	Patients 21 to 73 years with mild to moderate HTN (supine DBP of 95 to 115 mm Hg)	24 weeks	pressure and heart rate Secondary: Not reported	(7±2.5 and 7±2.0 mm Hg; P<0.01 for both). Both betaxolol and propranolol significantly reduced DBP from baseline (11±0.9 and 9±1.2 mm Hg; P<0.01 for both). Both betaxolol and propranolol significantly heart rate from baseline (6±1.3 and 7±1.1 bpm; P<0.01 for both). At the end of the study, there was not a significant difference in response between groups. Secondary: Not reported
Czuriga et al.[99] (2003) NEBIS Bisoprolol 5 mg QD vs nebivolol 5 mg QD	MC, PG, RCT, SB Patients 30 to 65 years with mild to moderate HTN, a DBP 95 to 110 mm Hg and a SBP ≤180 mm Hg at the end of the placebo run-in period who were either newly diagnosed or previously treated hypertensives and required a change of therapy in consequence of side-effects or poor compliance	N=273 16 weeks	Primary: Percentage of responders achieving DBP normalization (≤90 mm Hg) or a DBP reduction of at least 10 mm Hg and heart sitting rate Secondary: Adverse events, symptom questionnaire	Primary: There was not a significant difference between percentage of responders between the nebivolol group (92%) and the bisoprolol group (89.6%). There was not a significant difference in the mean change in blood pressure observed between the nebivolol and bisoprolol (SBP: -20.5±12.9 vs -20.0±12.0 mm Hg, respectively; P=0.7434) and DBP (-15.7±6.4 vs -16.0 ± 6.8 mm Hg, respectively; P=0.8230). There was not a significant difference in mean heart rate observed between the nebivolol (68.7±8.5 per minute) and the bisoprolol group (68.1±7.5 per minute). Secondary: There was not significant difference in rates of adverse events reported between the nebivolol (eight patients [5.8%]) and the bisoprolol group (12 patients [8.9%]; P>0.05). All adverse events were either mild (55%) or moderate (45%) in intensity. Both treatments demonstrated a significant reduction in the basal score index at visit 5 (nebivolol, -0.7 vs bisoprolol, -0.5; P<0.02), but there was no significant difference between treatment groups (P>0.05).
Stoschitzky et al.[100]	DB, PC, RCT, XO	N=16	Primary: Heart rate and	Primary: Compared to baseline, heart rate at exercise was decreased at three hours

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2006) Bisoprolol 10 mg on day 1, then 5 mg QD vs carvedilol 50 mg on day 1, then 25 mg BID vs nebivolol 10 mg on day 1, then 5 mg QD	Male patients between 22 and 34 years with a height between 177 and 189 cm, and body weight between 66 and 86 k	1 week	blood pressure at rest and exercise Secondary: Effects on nocturnal melatonin release, QOL	after the first dose by bisoprolol (-24%), carvedilol (-17%) and nebivolol (-15%); (P<0.05 for each group). Bisoprolol was significantly better than nebivolol (P<0.05). Compared to baseline, heart rate at exercise was decreased at 24 hours after the first dose by bisoprolol (-18%), carvedilol (12 hours; -15%) and nebivolol (-13%); (P<0.05 for each group). There was not a statistical significance observed between the groups. Compared to baseline, heart rate at exercise was decreased at 24 hours after the respective last dose at the end of one week of chronic administration by bisoprolol (-14%), carvedilol (12 hours; -15%) and nebivolol (-13%); (P<0.05 in all cases). There was not a statistical significance observed between the groups. All of the agents significantly decreased SBP both at rest and exercise at three and 24 hrs after the first dose as well at 24 hr after the last dose after seven days of chronic administration (P<0.05 in all cases). None of the agents had a significant effect on DBP at rest or at exercise. Secondary: Compared to placebo, nocturnal melatonin release was decreased by bisoprolol (-44%, P<0.05) whereas nebivolol (-16%) and carvedilol (-19%) had no effect. Total QOL with carvedilol (8.0±0.8) was slightly but significantly lower than that with placebo (8.6±0.4), nebivolol (8.5±0.6) and bisoprolol (8.4±0.5); (P<0.05 in all cases).
Lewin et al.[101] (1993) Bisoprolol and HCTZ 5-6.25 mg QD (fixed-dose combination product)	MC, PC Adult patients with stable mild to moderate (sitting DBP 95 to 114 mm Hg) essential HTN	N=36 4 weeks	Primary: Changes in 24-hr ambulatory daytime and nighttime blood pressure Secondary: Not reported	Primary: There were statistically significant reductions in blood pressure and pulse (P<0.01) at weeks two and four of treatment. There were statistically significant reductions (P<0.01) in 24 hr SBP and DBP, daytime and nighttime blood pressure, compared to the end of the placebo phase. There was a reduction in systolic and diastolic load also (P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				The combination was well tolerated. The scores from the overall QOL questionnaire indicated an improvement with the combination (P=0.02).
Benetos et al.[102] (2000) Bisoprolol and HCTZ 2.5-6.25 mg QD (fixed-dose combination product) vs amlodipine 5 mg QD	DB, MC, PG, RCT Patients over 60 years with supine SBP 160 to 210 mm Hg and DBP <90 mm Hg	N=164 12 weeks	Primary: Changes in blood pressure, heart rate, adverse events, QOL scores Secondary: Not reported	Primary: Both bisoprolol and HCTZ and amlodipine significantly reduced SBP (-20.0±13.7 and -19.6±14.2 mm Hg, respectively; P<0.001) and DBP (-4.5±7.4 and -2.4±8.4 mm Hg, respectively from baseline to week 12, but there was not a significant difference between the agents (SBP; P=0.85 and DBP; P=0.09). Bisoprolol and HCTZ significantly reduced heart rate from baseline, but amlodipine did not (-7.6±8.4 [P<0.001] and -0.2±11.4 bpm, respectively). Bisoprolol and HCTZ significantly reduced heart rate when compared to amlodipine (P=0.0001). Overall adverse events were not significantly different between the amlodipine and the bisoprolol and HCTZ group (39 and 40%, respectively). Adverse events reported included headache, leg edema, fatigue and bradycardia but severity of events was not reported. Overall QOL scores were not significantly different between the amlodipine and the bisoprolol and HCTZ group. Secondary: Not reported
Prisant et al.[103] (1995) Bisoprolol and HCTZ 2.5-6.25, 5-6.25, or 10-6.25 mg/day (fixed-dose combination product) vs	DB, MC, PG, RCT Patients ≥21 years with mild to moderate essential HTN, (average sitting DBP 95 to 114 mm Hg) each treatment was once daily and titrated to effect	N=218 17 weeks	Primary: Mean change from baseline in SBP and DBP, lab measurements, adverse events, QOL questionnaire Secondary: Not reported	Primary: Mean decreases in SBP and DBP from baseline were 13.4/10.7 mm Hg for bisoprolol and HCTZ patients, 12.8/10.2 mm Hg for amlodipine patients, and 7.3/6.6 mm Hg for enalapril patients. The hypotensive effects were significant for all three groups (P<0.001). SBP and DBP mean changes from baseline for the bisoprolol and HCTZ group and the amlodipine group were greater than the change from baseline for the enalapril group (P<0.01). Response rates (DBP ≤90 mm Hg or ≥10 mm Hg decrease from baseline)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
enalapril 5, 10, or 20 mg vs amlodipine 2.5, 5, or 10 mg				were 71% for the bisoprolol and HCTZ group, 69% for the amlodipine group, and 45% for the enalapril group. The response rates for the bisoprolol and HCTZ and the amlodipine groups differed significantly from the enalapril group (P<0.01). Twenty nine percent of bisoprolol patients had adverse experiences compared to 42% of amlodipine patients (P=0.12). Nearly 47% of enalapril patients had adverse experience compared to bisoprolol (P=0.04). Adverse events reported included headache, fatigue, peripheral edema, and dizziness. Drug related adverse events were 16% for the bisoprolol and HCTZ patients, 21% for the amlodipine patients, and 23% for the enalapril patients. There was no significant difference between the groups. Enalapril demonstrated a mean decrease from baseline of 7.9 mg/dL for TC (P=0.02 vs amlodipine) and 6.6 mg/dL for LDL-C (P=0.04 vs amlodipine) which were not significantly different from the increase from the bisoprolol and HCTZ group of 1.7 mg/dL (P=0.07 vs enalapril) for TC and +0.6 mg/dL in LDL-C. However, the increase in TGs was highest for bisoprolol and HCTZ-treated patients compared to amlodipine- and enalapril-treated patients (P=0.08, for bisoprolol and HCTZ vs enalapril). There was not a significant difference from baseline or between treatment groups in QOL scores: 0.9 for the bisoprolol and HCTZ group, 0.5 for the amlodipine group, and 2.3 for the enalapril group.
Frishman et al.[104] (1994) Bisoprolol 2, 5, 10, or 40 mg QD vs HCTZ 6.25 or 25 mg QD	DB, MC, PC, RCT Patients 21 years and older with mild to moderate essential HTN whose weight was 35% of the ideal for height and frame and mean sitting DBP was stable and	N=512 12 weeks	Primary: Changes in DBP and SBP Secondary: Not reported	Primary: All treatment groups (all doses) of bisoprolol, HCTZ and the combination of bisoprolol and HCTZ significantly reduced sitting DBP from baseline (P<0.01). The reduction in blood pressure was significantly greater as the doses of the bisoprolol, HCTZ and the combination of bisoprolol-HCTZ were increased (P<0.05). The combination bisoprolol and HCTZ significantly reduced sitting DBP compared to the separate agents as monotherapy (P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs bisoprolol plus HCTZ, all possible combinations	between 95 to 115 mm Hg			With higher doses of HCTZ, there was a significantly higher incidence of hypokalemia, defined as potassium <3.5 mmol/L (P<0.01). Incidence of hyperuricemia also significantly increased with the increase in HCTZ dose (P<0.01). Adverse events associated with hypokalemia and hyperuricemia were not reported. As the dose of bisoprolol was increased, the frequency and severity of adverse events reported significantly increased (P<0.05). Adverse events reported included asthenia, diarrhea, dyspepsia and somnolence, but severity of effects was not reported. Secondary: Not reported
Frishman et al.[105] (1995) Bisoprolol 5 mg QD vs HCTZ 25 mg QD vs bisoprolol and HCTZ 5-6.25 mg QD (fixed-dose combination product) vs placebo	DB, MC, PC, PG, RCT Patients ≥21 years with mild to moderate (stage II or II) systemic HTN whose body weight was not >10% below or 35% above the ideal weight for height and frame, and were off all antihypertensive medications before study entry and sitting DBP was 95 to 115 mm Hg on 3 consecutive weekly visits	N=547 10 weeks	Primary: Changes in blood pressure and adverse events Secondary: Not reported	Primary: All active treatment groups significantly reduced sitting DBP and SBP from baseline compared to placebo (P<0.01). Addition of HCTZ 6.25 mg contributed significantly to the blood pressure lowering effects of bisoprolol 5 mg. The combination bisoprolol and HCTZ 5-6.25 mg produced a significantly greater reduction in mean sitting DBP from baseline (-12.6±0.5 mm Hg) compared to bisoprolol 5 mg alone (-10.5±0.5 mm Hg; P=0.02) and HCTZ 25 mg alone (-8.5±0.5 mm Hg; P<0.01). Bisoprolol 5 mg monotherapy was significantly better a reducing DBP compared to HCTZ 25 mg alone (P=0.03). The combination bisoprolol and HCTZ 5-6.25 mg produced a significantly greater reduction in mean sitting SBP from baseline (-15.8 mm Hg) compared to bisoprolol 5 mg alone (-10 mm Hg; P<0.01) and HCTZ 25 mg alone (-15.8 mm Hg; P<0.01). There was not a significant difference in mean reduction between bisoprolol 5 mg alone and HCTZ 25 mg alone. Bisoprolol and HCTZ 5-6.25 mg in combination had a 73% response rate compared to 61% for the bisoprolol group and 47% for the HCTZ group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Bisoprolol and HCTZ 5-6.25 mg in combination was found to be significantly more effective compared to bisoprolol 5 mg or HCTZ 25 mg in all subgroups of patients regardless of age, race, gender, or smoking history (P>0.05 for all comparisons). Bisoprolol and HCTZ 5-6.25 mg in combination did not have an increase in frequency or severity of adverse events. The adverse events were comparable to that in the placebo group and frequency among groups was not significant. The most common adverse events reported were headache, dizziness, fatigue, and cough. Significantly greater number patients in the HCTZ 25 mg group (6.5%) experienced hypokalemia (potassium <3.4 mEq/L) compared to the bisoprolol 5 mg group (0.7%; P<0.01), the bisoprolol and HCTZ combination group (0.7%; P<0.01), and placebo (0%; P<0.01). Hyperglycemia occurred in 7.4% of patients in the HCTZ 25 mg group, which was significantly higher than in the placebo group (5.2%; P=0.03). Also, the incidence of hyperuricemia (uric acid >7.5 mg/dL) was significantly higher in the HCTZ 25 mg group (24.4%) compared to placebo (2.7%; P<0.01). Secondary: Not reported
Williams et al.[106] (2015) PATHWAY-2 Twelve weeks of once daily treatment with each of spironolactone (25 to 50 mg), bisoprolol (5 to 10 mg), doxazosin modified release (4	DB, PC, XO Patients 18 to 79 years of age with seated clinic SBP ≥ 140 mmHg (or ≥135 mmHg for patients with diabetes) and home SBP (18 readings over four days) ≥130 mmHg, despite treatment for at least three	N=335 12 months	Primary: Average home SBP, recorded in the morning and the evening in triplicate, on four consecutive days before study visits Secondary: Clinic SBP, BP control rates, adverse events	Primary: The average reduction in home SBP by spironolactone was significantly greater compared to placebo (–8.70 mmHg; 95% CI, −9.72 to −7.69; P<0.0001), compared to the mean of the other two active treatments (doxazosin and bisoprolol; −4.26; 95% CI, –5.13 to −3.38; P<0·0001), and compared to the individual treatments; versus doxazosin (–4.03; 95% CI, –5.04 to −3.02; P<0.0001) and versus bisoprolol (–4.48; 95% CI, –5.50 to −3.46; P<0.0001). Secondary: The results for seated clinic SBP largely mirror those seen with home SBP except that there was a large placebo effect on clinic BP that was not seen with home BP measurement.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
to 8 mg), and placebo, in addition to their baseline blood pressure drugs	months with maximally tolerated doses of three drugs (an ACE or ARB, a CCB, and a diuretic)			Overall 219 (68.9%; 95% CI, 63.6 to 73.8) of 314 patients achieved target home SBP of <135 mmHg. 58% of patients had their BP controlled with spironolactone, which was significantly greater than rates for other treatments (P<0.001 when compared to doxazosin, bisoprolol, and placebo). Most patients who were controlled by doxazosin or bisoprolol had a still greater fall in blood pressure on spironolactone, which was consequently the most effective treatment in almost 60% of patients. This was at least three times the proportion in whom doxazosin or bisoprolol were the most effective. All active treatments were well tolerated with similar low rates of adverse events and withdrawals due to adverse events.
Hamaad et al.[107] (2007) Carvedilol 3.125 to 25 mg BID vs bisoprolol 1.25 to 10 mg QD	RCT Patients with stable LVEF of <40% and treated with diuretic and ACE inhibitor or ARB	N=31 12 weeks	Primary: Blood pressure, heart rate responses and both time and frequency domain heart rate variability Secondary: Not reported	Primary: Carvedilol significantly reduced DBP from baseline to week 12 of therapy (stage 6), but bisoprolol did not: 10±16 mm Hg (P=0.045) and 7±16 mm Hg, respectively (P=0.159), but there was not a significant difference between groups. Both carvedilol and bisoprolol significantly reduced SBP from baseline to week 12 of therapy (stage 6): 18±28 mm Hg (P=0.045) and 12±16 mm Hg, respectively (P<0.003) but there was not a significant difference between groups. Both carvedilol and bisoprolol significantly decreased mean heart rate from baseline to week 12 of therapy (stage 6): 25±20 bpm and 23±10 bpm, respectively (P<0.01 for both agents vs baseline) but there was not a significant difference between groups (P=0.708). Neither carvedilol nor bisoprolol significantly increased four of the five heart rate variability indices measured including SDNN, RMSSD, low frequency power or high frequency power. But both carvedilol and bisoprolol significantly increased triangular index from baseline to week 12 of therapy (stage 6): 7±6 (P<0.01) and 5±6 (P=0.01), respectively, but there was not a significant difference between groups. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Erdogan et al.[108] (2011) Carvedilol 25 mg QD for 1 month vs nebivolol 5 mg QD for 1 month All patients went through a 10 day placebo run in period.	DB, PC, PRO, RCT, XO Patients with mild to moderate HTN	N=20 2 months	Primary: Blood pressure, heart rate Secondary: Safety	Primary: Treatment with carvedilol (133.8±9/86.6±8.6 mmHg) and nebivolol (134±8.7/85.6±7.4 mmHg) significantly decreased SBP and DBP compared to placebo (143.9±8.9/94.4±9.2 mmHg; P<0.05). There was no difference between carvedilol and nebivolol (P>0.05). Mean heart rate was significantly decreased after initiating treatment with carvedilol (70.2±5.2 bpm) and nebivolol (64.9±3.9 bpm) compared to placebo (78.8±5.2; P<0.05). Secondary: No adverse events were reported with either treatment.
Saunders et al.[109] (1987) Labetalol 100 to 800 mg BID vs propranolol 40 to 320 mg	DB, PG Patients with mild to moderate HTN	N=153 Duration not specified	Primary: Blood pressure, heart rate Secondary: Not reported	Primary: Labetalol was significantly better than propranolol at the end of monotherapy at lowering DBP (P<0.05) but there was no difference in lowering SBP. Propranolol was significantly better at lowering heart rate compared to labetalol (P<0.01). No difference in the decrease in blood pressure after a diuretic was added. Secondary: Not reported
McAreavey et al.[110] (1984) Labetalol 200 mg QD up to 1,600 mg BID vs	DB, PG, RCT Patients with inadequately controlled HTN while receiving atenolol 100 mg/day and bendrofluazide* 5 mg/day	N=238 6 months	Primary: Comparative safety and efficacy, target blood pressure <140/95 mm Hg Secondary: Not reported	Primary: Target blood pressure was reached in 25% of patients receiving hydralazine, 23% of patients receiving minoxidil, 19% of patients receiving prazosin, 17% of patients receiving methyldopa and zero percent of patients receiving placebo (P values not reported). Labetalol had the highest withdrawal rate compared to the other treatments with 78% (P<0.05). Minoxidil had the second highest withdrawal rate with 57% (P<0.05), due to fluid retention. There were no significant differences

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
prazosin 0.5 mg QD up to 10 mg BID vs hydralazine 12.5 mg QD up to 100 mg BID vs methyldopa 125 mg QD up to 1,000 mg BID vs placebo Minoxidil as add on therapy was given to men only. Doses were titrated upward at 2 week intervals until target blood pressure or maximum dose was reached.				in withdrawal rates among the other treatments. Secondary: Not reported
Wright et al.[111] (2002) AASK Metoprolol 50 to	DB, MC, RCT Patients were self-identified African Americans aged 18	N=1,094 3-6.4 years	Primary: Rate of change in GFR (grouped by usual blood pressure [MAP	Primary: No significant difference in primary outcome was reported between the usual blood pressure group compared to the lower blood pressure group (P=0.24).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
200 mg/day vs ramipril 2.5 to 10 mg/day vs amlodipine 5 to 10 mg/day	to 70 years with HTN and a GFR between 20 and 65 mL/min/ 1.73 m^2 and no other identified cause of renal insufficiency		goal 102 to 107 mm Hg] vs lower blood pressure [≤92 mm Hg]) Secondary: Clinical composite outcome (reduction in GFR by 50% or more, ESRD, or death)	None of the drug group comparisons showed consistently significant differences in the GFR slope. Secondary: The lower blood pressure goal did not significantly reduce the rate of the clinical composite outcome (risk reduction for lower blood pressure group, 2%; 95% CI, -22 to 21; P=0.85). Ramipril resulted in significant risk reductions in the clinical composite outcomes compared to amlodipine (38%; 95% CI, 14 to 56; P=0.004) and metoprolol (22%; 95% CI, 1 to 38; P=0.04). There was no significant difference in the clinical composite outcome between the amlodipine and metoprolol groups.
Dafgard et al.[112] (1981) Metoprolol and HCTZ 200-25 mg QD in the morning (fixed-dose combination product) vs HCTZ 50 mg QD in the morning vs HCTZ 25 mg QD in the morning	DB, MC, RCT Patients with essential HTN (WHO stages I or II) not adequately controlled (≥160/95 mm Hg) on HCTZ 25 mg/day	N=31 32 weeks	Primary: Blood pressure, heart rate, adverse events, laboratory values Secondary: Not reported	Primary: After the eight week run-in period with HCTZ 25 mg alone, the mean supine blood pressure was significantly reduced from 183/110 to 172/103 mm Hg (P<0.01/P<0.01). The increased dose of HCTZ 50 mg following the run-in period did not further significantly reduce the mean blood pressure (165/104 mm Hg). A small but statistically significant reduction in supine heart rate was seen when the HCTZ dose was increased from 25 to 50 mg (82 down to 78 bpm; P<0.05). After the 12 week double-blind period, the mean supine blood pressure was 153/98 mm Hg in the HCTZ 50 mg group. After the 12 week follow-up period, there was not any additional decrease in blood pressure (153/97 mm Hg). Fixed-dose combination product of metoprolol and HCTZ produced a significant reduction in supine blood pressure after 12 weeks of therapy from 172/105 mm Hg on HCTZ 25 mg alone to 154/97 mm Hg on the combination therapy (P<0.001/P<0.01). Similar results were found with the standing blood pressure reductions, from 165/108 to 147/97 mm Hg (P<0.001/P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				After the eight week run-in period, the supine heart rate was 80 bpm which decreased to 64 bpm with the metoprolol and HCTZ fixed-dose combination (P<0.001). The values for standing heart rate demonstrated similar significant reductions (85 to 66 bpm; P<0.001). After the additional 12 week follow-up, the patients in the metoprolol and HCTZ fixed-dose combination group did not demonstrate a significant further reduction in heart rate or blood pressure in any position. Both agents were tolerated and the most common adverse events reported included insomnia, headache, tiredness, and shortness of breath. The majority of events were mild, few were moderate, and none were severe. The only significant changes in laboratory values occurred with the HCTZ 25 and 50 mg groups, where an increase in serum uric acid was observed from 0.30 to 0.34 and 0.35 mmol/L, respectively (P<0.01 and P<0.05; respectively). Secondary: Not reported
Smilde et al.[113] (1983) Metoprolol 400 mg QD in the morning for 5 weeks, followed by metoprolol and HCTZ 200-25 mg QD in the morning (fixed-dose combination product) (group 1) vs metoprolol and HCTZ 200-25 mg	DB, PG, RCT, XO Patients <65 years with essential HTN (supine DBP ≥95 mm Hg) not controlled on metoprolol 200 mg alone	N=37 15 weeks	Primary: Changes in DBP, SBP, and heart rate Secondary: Not reported	Primary: Both group 1 and 2 significantly reduced DBP (P<0.01) from baseline and the two groups were not significantly different from each other. The combination products significantly reduced SBP from baseline (P<0.05, P<0.01 depending on comparison) Group 2 significantly reduced heart rate at the end of the study compared to baseline (P<0.05). Clinically relevant changes in laboratory parameters or mean body weight were not observed between the groups. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QAM for 5 weeks (fixed-dose combination product), followed by metoprolol 400 mg QD in the morning for 5 weeks (group 2)				
Liedholm et al.[114] (1981) Metoprolol and HCTZ 100-12.5 mg BID (fixed-dose combination product) (group A) vs metoprolol and HCTZ 100-25 mg BID (fixed-dose combination product) (group B) <u>Extended Study:</u> Metoprolol and HCTZ 100-12.5 mg, 2 tablets QD in the morning (fixed-dose combination product)	RCT Patients 18 to 72 years with mild to moderate essential HTN (WHO I or II) <u>Extended Study:</u> OL Those patients who participated in the initial trial, had poor blood pressure control on existing antihypertensive therapy, and were being treated with a β-blocker and additional diuretic therapy	N=55 12 weeks <u>Extended Study:</u> N=49 6 months	Primary: Change in blood pressure Secondary: Not reported	Primary: In group A, there was a significant decrease in supine blood pressure from 189/112 to 172/105 mm Hg with metoprolol monotherapy and further reduction to 148/92 mm Hg with the metoprolol and HCTZ 100-12.5 mg (P<0.001/P<0.001). In group B, there was a significant decrease in supine blood pressure from 184/111 to 170/104 mm Hg with metoprolol monotherapy and further reduced to 152/96 mm Hg with metoprolol and HCTZ 100-25 mg (P<0.01/P<0.05) after 12 weeks. Supine heart rate fell in group A from 78 to 68 bpm with metoprolol monotherapy (P<0.001). No further heart rate reduction was noted with the metoprolol and HCTZ 100-12.5 mg. In group B, supine heart rate fell from 76 to 69 bpm (P<0.05). No further heart rate reduction was seen with metoprolol and HCTZ 100-25 mg. In group A, serum sodium fell from 143 to 140 mmol/L (P<0.01). In group B, serum potassium fell with from 4.4 to 4.0 mmol/L (P<0.001). <u>Extended Study:</u> After six months of extended the therapy, there was no further significant reductions in supine or standing blood pressure, but there was a reduction in standing DBP from 97 to 95 mm Hg (P<0.05).
Materson et al.[115] (1990)	DB, MC, RCT Men ≥60 years with	N=690 12 months	Primary: The average reduction in SBP	Primary: Across all four treatments, there was an additional average reduction in BP of 13.1/10.6 mm Hg. The average reduction in SBP from baseline to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Metoprolol 50, 100 or 200 mg BID vs hydralazine 25, 50 or 100 mg BID vs methyldopa 250, 500 or 1,000 mg BID vs reserpine 0.05, 0.10 or 0.25 mg QD All patients received HCTZ 25 to 100 mg QD.	HTN not currently receiving antihypertensive therapy and DBP 90 to 114 mm Hg and SBP <240 mm Hg or a DBP <100 mm Hg and a SBP <240 mm Hg if currently taking antihypertensive therapy and the blood pressure criteria was met after ≥2 weeks without medication		and DBP, the number of patients achieving the goal blood pressure, the average change in heart rate Secondary: The rates of drug intolerances, adverse effects	endpoint for hydralazine, methyldopa, metoprolol and reserpine were -11.5±10.1 (P<0.001), -15.0±13.7 (P<0.001), -13.0±15.4 (P<0.001) and -12.7±11.5 (P<0.001), respectively. There was no significant difference in SBP reductions among the different treatments (P=0.43). The average reduction in DBP from baseline to endpoint for hydralazine, methyldopa, metoprolol and reserpine were -11.3±5.9 (P<0.001), -10.6±6.3 (P<0.001), -10.6±6.7 (P<0.001) and -9.8±6.3 (P<0.001), respectively. There was no significant difference in DBP reductions among the different treatments (P=0.59). The average change in heart rate from baseline to endpoint for hydralazine, methyldopa, metoprolol and reserpine were 1.4±10.5 (P value not significant), -1.6±9.3 (P value not significant), 15.9±11.9 (P<0.05) and -7.9±10.7 (P<0.05), respectively. There was a significant difference in change in heart rate among the different treatments (P<0.001). The percentage of patients achieving the goal blood pressure at endpoint with hydralazine, methyldopa, metoprolol and reserpine were 85.3, 81.7, 76.9 and 72.3%, respectively (P=0.28). Secondary: Drug intolerance, defined as adverse effects prompting dose reduction or discontinuation, was present in 23.3% of patients not achieving goal blood pressure compared to 2.8% of those who did (P<0.001). This was significant with hydralazine, methyldopa and metoprolol, but not with reserpine. There were 27 (10%) treatment discontinuations due to adverse effects (hydralazine [n=3], methyldopa [n=8], metoprolol [n=9] and reserpine [n=7]). There were two treatment discontinuations with methyldopa and one with reserpine due to depression. The overall incidence of volunteered moderate or severe adverse effects, not prompting treatment discontinuation, was significantly greater (P<0.01) with methyldopa (31%) and hydralazine (25%) compared to reserpine (15%) or metoprolol (9%).
Greathouse.[116]	DB, PC, PG, RCT	N=811	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2010) Nebivolol 5, 10 or 20 mg QD vs placebo All patients entered a 4 to 6 week washout, SB, placebo run in period.	Patients ≥18 years of age with stage I to II HTN (average sitting DBP ≥95 and ≤109 mm Hg)	12 weeks	Change in mean sitting DBP at trough drug concentration (24±2 hours after the previous morning's dose) Secondary: Mean changes in trough sitting SBP, responder rate (mean trough SBP <90 mm Hg or a decrease of ≥10 mm Hg from baseline), safety and tolerability	Least squares mean reductions in trough sitting DBP at week 12 were significantly greater with all doses of nebivolol compared to placebo (P=0.002 for 5 mg and P<0.001 for 10 and 20 mg). All doses of nebivolol reduced peak sitting DBP in a dose-dependent manner. The least squares mean reductions in peak sitting DBP following treatment with 5, 10, and 20 mg of nebivolol were -10.5, -11.6, and -12.2 mm Hg (P<0.001 vs placebo for all). Secondary: All doses of nebivolol resulted in least squares mean reductions in trough sitting SBP from baseline, with only the 20 mg dose reaching significance compared to patients receiving placebo (P<0.001). All doses of nebivolol reduced peak sitting SBP in a dose-dependent manner. The least squares mean reductions with nebivolol in peak sitting SBP were -7.7, -10.7 and -4.7 mm Hg (P=0.004 vs placebo for 10 mg and P<0.001 vs placebo for 20 mg). Significantly more patients receiving nebivolol were treatment responders compared to placebo (66.0 [P=0.009 vs placebo], 66.8 [P=0.005 vs placebo] and 68.9% [P=0.002 vs placebo] vs 49.3%). A total of 27 (36.0%) and 311 (42.5%) patients receiving placebo and nebivolol experienced an adverse event. The most commonly reported adverse events for the combined nebivolol group (all doses) compared to the placebo group were headache (7.5 vs 5.3%), fatigue (3.8 vs 1.3%) and nasopharyngitis (3.7 vs 4.0%).
Neutel et al.[117] (2010) Nebivolol 5, 10 or 20 mg/day vs placebo	DB, PC, PG, RCT Patients ≥18 years of age with stage I to II HTN who were inadequately controlled by antihypertensive medication (SBP ≥90 and ≤109 mm	N=669 12 weeks	Primary: Change in mean clinic sitting DBP at trough (24±3 hours after previous morning's dose) Secondary: Change in mean	Primary: Addition of nebivolol to background antihypertensive therapy led to significant additional blood pressure reductions compared to placebo. Nebivolol 5, 10, and 20 mg significantly lowered trough sitting DBP by -3.3, -3.5, and -4.6 mm Hg, respectively (P<0.001 for all doses). Secondary: Nebivolol 5, 10 and 20 mg significantly lowered trough sitting SBP by -5.7, -3.7, and -6.2 mm Hg, respectively (P<0.001 for 5 and 20 mg and P=0.015 for 10 mg).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	Hg) and stable on a regimen of antihypertensive medications consisting of ≥1 and ≤2 of an ACE inhibitor, ARB or diuretic		trough sitting SBP and mean sitting DBP, change in mean sitting SBP at peak (two to three hours after dosing), mean peak and trough supine and standing DBP and SBP, mean 24 hour DBP and SBP as measured by ambulatory blood pressure monitoring, responder rate (sitting SBP <90 mm Hg or an absolute reduction ≥10 mm Hg)	Reductions in trough blood pressure in the standing and supine positions were comparable to sitting blood pressure reductions for all nebivolol doses. All doses of nebivolol also significantly reduced peak sitting DBP (-3.2, -4.0, and -4.3 mm Hg) and sitting SBP (-5.7, -5.6, and -5.9 mm Hg) at week 12 compared to placebo (P<0.001 for both). Reductions from baseline to week 12 in peak blood pressure with nebivolol in both supine and standing positions were consistent with those for sitting DBP and sitting SBP (data not reported). After 12 weeks, the proportion of patients responding to treatment was significantly higher with nebivolol 5 mg (53.0%; P=0.028), 10 mg (60.1%; P=0.001) and 20 mg (65.1%; P<0.001) compared to placebo (41.3%). In addition, a significantly higher percentage of patients receiving nebivolol achieved blood pressure control (<140/90 mm Hg) (43.0, 41.3 and 52.7 vs 29.3%; P≤0.029).
Weiss et al.[118] (2011) Nebivolol 1.25 to 30 or 40 mg/day vs placebo	Pooled analysis of 3 PC, RCT, SB Patients with stage I-II HTN	N=2,016 ≥12 weeks	Primary: Mean change from baseline in sitting DBP, sitting SBP, and heart rate at 12 weeks Secondary: Safety	Primary: Compared to placebo, reductions in DBP, SBP, and heart rate were significantly greater with nebivolol at the recommended dosages of 5-30/40 mg/day (P<0.001 for all). Secondary: The most commonly reported adverse events were headache (7.1 vs 5.9%), fatigue (3.6 vs 1.5%), and nasopharyngitis (3.1 vs 4.4%).
Rosei et al.[119] (2003) Nebivolol 5 mg QD vs	DB, MC, PG, RCT Patients between 24 and 65 years with mild to moderate uncomplicated essential HTN that was newly	N=65 12 weeks	Primary: Response rates, changes in sitting blood pressure Secondary: Standing blood pressure, sitting	Primary: There was not a significant difference in response rates observed between the two treatment groups. Both treatment groups significantly reduced sitting SBP (P<0.0001) and DBP (P<0.0001) throughout the study compared to baseline but there were no significant differences observed between the treatment groups at most visits, but at week eight, DBP was significantly lower in the nebivolol

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
lisinopril 20 mg QD	diagnosed, or previous antihypertensive therapy was withdrawn at >1 month before active treatment, and had a sitting DBP of >95 and <114 mm Hg		and standing heart rate	group compared to the lisinopril group (P<0.05). Secondary: There was not a significant difference observed between treatment groups in standing blood pressure measurements. Both treatment groups significantly reduced sitting heart rate (P<0.01) throughout the study compared to baseline but there were no significant differences observed between the treatment groups at most visits, but at week eight, heart rate were significantly lower in the nebivolol group compared to the lisinopril group (P<0.05).
Mazza et al.[120] (2002) Nebivolol 2.5 to 5 mg QD vs amlodipine 5 to 10 mg QD	DB, MC, PG, RCT Patients between 65 to 89 years of age with mild to moderate essential HTN and DBP ranging from 95 to 114 mm Hg	N=168 16 weeks	Primary: Change in sitting blood pressure, response rates Secondary: Standing blood pressure changes, standing and sitting heart rate changes	Primary: There was not a significant difference observed between the amlodipine and nebivolol treatments groups in changes in sitting DBP (blood pressure values and P values not reported). At weeks four and eight, a slightly lower sitting SBP was observed in per-protocol patients in the amlodipine groups vs those in the nebivolol group (blood pressure values not reported, P<0.005). Response rates were not significantly difference between the amlodipine group and the nebivolol group (86 vs 88%, respectively). The percentage of patients who reached normalization (blood pressure <140/90 mm Hg) was no significant between the amlodipine and the nebivolol groups (47 vs 50%). Secondary: There were significant differences in standing blood pressure observed between the groups. Heart rate was significantly lower in the nebivolol group compared to the amlodipine group at all treatment visits (P<0.001). Patients in the amlodipine group experienced a significantly greater rate of headache (seven vs five patients) and ankle edema (12 vs zer0 patients) compared to the patients in the nebivolol group (P<0.05 for both).
Van Bortel et al.[121] (2005)	DB, MC, PG, RCT	N=314	Primary: Effects on blood	Primary: At the end of 12 weeks, both nebivolol and losartan significantly reduced

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Nebivolol 5 mg QD vs losartan 50 mg QD If after 6 weeks, DBP was not normalized, then HCTZ 12.5 mg QD was added to therapy	Patients <70 years of age with DBP at randomization between 95 and 114 mm Hg	12 weeks	pressure, overall QOL Secondary: Comparison of different aspects of QOL	SBP compared to baseline (P<0.0001 for both), but the agents were not significantly different from each other. Both agents also significantly decreased DBP compared to baseline (P<0.0001), but nebivolol significantly reduced DBP compared to losartan (P<0.02). At the end of 12 weeks, both nebivolol and losartan significantly improved QOL scores compared to baseline (P<0.007), but the agents were not significantly different from each other. Secondary: At week 12 there was not a significant difference observed in the individual questions of the QOL questionnaire between the groups. Questions inquired about headaches, lightheadedness, sleepiness, flushing, and sexual function.
Van Bortel et al.[122] (2008) Nebivolol vs ACE inhibitor, ARB, β-blocker, calcium channel blocker, or placebo	MA 12 RCTs involving >25 patients with essential HTN where nebivolol 5 mg QD was compared to placebo or other active drugs for >1 month	N=2,653 Duration varied	Primary: Antihypertensive effect and tolerability Secondary: Not reported	Primary: Overall, higher response rates were observed with nebivolol than all other antihypertensive agents combined (OR, 1.41; 95% CI, 1.15 to 1.73; P=0.001) and compared to the ACE inhibitors (OR, 1.92; 1.30 to 2.85; P=0.001), but response rates to nebivolol were similar to β-blockers (OR, 1.29; 95% CI, 0.81 to 2.04; P=0.283), calcium channel blockers (OR, 1.19; 95% CI, 0.83 to 1.70; P=0.350) and losartan (OR, 1.35; 95% CI, 0.84 to 2.15; P=0.212). Overall, a higher percentage of patients obtained normalized blood pressure with nebivolol compared to the other antihypertensive agents combined (OR, 1.35; 95% CI, 1.07 to 1.72; P=0.012). A higher percentage of patient receiving nebivolol obtained normalized blood pressure compared to losartan (OR, 1.98; 95% CI, 1.24 to 3.15; P=0.004) and calcium channel blockers (OR, 1.96; 95% CI, 1.05 to 1.96; P=0.024), but not when compared to other β-blockers (OR, 1.29; 95% CI, 0.81 to 1.65; P=0.473). Overall, the percentage of adverse events was significantly lower with nebivolol compared to the other antihypertensive agents combined (OR, 0.59; 95% CI, 0.48 to 0.72; P<0.001) and similar to placebo (OR, 1.16;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				95% CI, 0.76 to 1.67; P=0.482). In comparing nebivolol to the individual treatments, nebivolol had a lower percentage of adverse events compared to losartan (OR, 0.52; 95% CI, 0.30 to 0.89; P=0.016), the other β-blockers (OR, 0.56; 95% CI, 0.36 to 0.85; P=0.007) and calcium channel blockers (OR, 0.49; 95% CI 0.33 to 0.72; P<0.001), but was similar to ACE inhibitors (OR, 0.75; 95% CI 0.52 to 1.08). Secondary: Not reported
Veterans Administration Cooperative Study Group on Antihypertensive Agents[123] (1983) Nadolol 80 to 240 mg QD in the morning vs bendro-flumethiazide 5 to 10 mg* QD in the morning vs nadolol and bendro-flumethiazide*	DB, RCT Men 20 to 69 years with pretreatment DBP of 95 to 114 mm Hg	N=365 12 weeks	Primary: Changes in blood pressure, change in blood pressure among races, heart rate, adverse events, laboratory values Secondary: Not reported	Primary: DBP of <90 mm Hg was achieved in 49% of the nadolol patients, 46% of the bendroflumethiazide patients, and 85% of the combination patients. There was a significantly higher percentage of patients who achieved the DBP goal compared to the nadolol alone group and bendroflumethiazide group alone (P<0.01 for both). The reduction in SBP was significantly greater in the combination group compared to the nadolol alone and bendroflumethiazide group (-25.3±1.4, -10.5±1.6, and -17.4±1.7 mm Hg, respectively; P<0.001 for both) and bendroflumethiazide produced a significantly greater reduction compared to nadolol alone (P<0.01). The reduction of DBP in white patients was significantly greater than the decrease in African American (decrease of 15.6 vs 9.6 mm Hg, respectively; P<0.001). In addition, 77% of white patients achieved DBP of <90 mm Hg compared to only 31% of African American patients (P<0.001). Adverse events were infrequent. The most common were impotence, lethargy, weakness, and postural dizziness, which occurred more often with bendroflumethiazide than nadolol. Significant reductions in average heart rate from baseline were observed with nadolol alone (decrease by 16.1 bpm; P<0.001) and with the combination product (decrease by15.8 bpm; P<0.001). Serum potassium levels significantly decreased from baseline in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				bendroflumethiazide group by -0.57±0.06 mEq/L (P<0.001) and in the combination group by -0.44±0.05 mEq/L (P<0.001). Serum uric acid levels significantly increased from baseline in the bendroflumethiazide group by 1.7±0.2 mg/dL (P<0.001), in the nadolol group by 0.4±0.1 mg/dL (P<0.01) and in the combination group by -1.9±0.1 mg/dL (P<0.001). Fasting glucose levels significantly increased from baseline in the bendroflumethiazide group by 6.1±2.1 mg/dL (P<0.001) and in the combination group by 7.4±1.1 mg/dL (P<0.001). Cholesterol significantly increased from baseline in the bendroflumethiazide group by 11.5±4.3 mg/dL (P<0.001). TGs significantly increased from baseline in the bendroflumethiazide group by 34.6±14.8 mg/dL (P<0.01), in the nadolol group by 38.7±13.2 mg/dL (P<0.01) and in the combination group by 67.8±11.9 mg/dL (P<0.001). Secondary: Not reported
Frick et al.[124] (1978) Penbutolol 40 mg BID vs propranolol 160 mg BID	DB, XO Patients 29 to 64 years of age with HTN	N=20 13 weeks	Primary: Blood pressure, heart rate Secondary: Not reported	Primary: Penbutolol significantly reduced supine and standing blood pressures (both SBP and DBP) from baseline (P<0.05). Propranolol also significantly reduced blood pressures from baseline (SBP: P<0.02 and diastolic: P<0.01), but there was not significant difference between agents. Penbutolol significantly reduced supine and standing heart rates from baseline (from 76±10 to 61±9; P<0.001 and from 85±13 to 67±8; P<0.001, respectively. Propranolol also significantly reduced heart rates from baseline (to 59±8; P<0.001 and to 63±7; P<0.001, respectively), but there was not significant difference between agents. Secondary: Not reported
Finnerty et al.[125]	SB	N=59	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1979) Propranolol 80 mg to 320 mg QD vs reserpine 0.125 mg to 0.25 mg QD vs methyldopa 500 mg to 2,000 mg QD All patients received hydro-flumethiazide* 50 or 100 mg QD.	Patients with HTN unresponsive to hydroflumethiazide alone	9 weeks	Percentage of patients achieving a DBP below 90 mm Hg Secondary: Not reported	At study endpoint, the DBP below 90 mm Hg was achieved in all 20 patients (100%) treated with hydroflumethiazide plus reserpine, 13 of the 19 patients (68.4%) treated with hydroflumethiazide plus methyldopa, and in 16 of the 20 patients (80%) treated with hydroflumethiazide plus propranolol. Secondary: Not reported
VA Cooperative Study[126] (1977) Propranolol 40 to 160 mg TID (P), propranolol 40- to 160 mg TID plus HCTZ 35 mg (P+T), propranolol 40 to 160 mg TID plus hydralazine 35 mg (P+H), or propranolol 40 to 160 mg TID plus HCTZ 35 mg plus hydralazine 35 mg	DB, RCT Men 18 to 59 years with DBP of 90 to 114 mm Hg	N=450 18 months	Primary: Percent of patients who achieved a DBP <90 mm Hg at 6 months, heart rate, withdrawal rate Secondary: Not reported	Primary: At six months, significantly more patients in the R+T arm (88%) attained a DBP <90 mm Hg and ≥5 mm Hg less than the initial blood pressure compared to the P arm (52%; P<0.01) and the P+H arm (72%; P<0.05). The other arms: P+T (81%) and P+T+H (92%) were not significantly different than the R+T arm. The 12 and 18 month results do not have the statistical validity of the six months results due to the reduced sample size. The following percentage of patients attained DBP <90 mm Hg and ≥5 mm Hg less than the initial pressure: R+T=89.1 and 82.6%, P=59.5 and 58.1%, P+T=86.0 and 86.4%, P+H=67.4 and 76.1%, and P+T+H=89.4 and 91.8%. There was not a significance difference in heart rate reductions at six and 18 months between the groups (R+T=5.0±1.3 and 5.0±1.3 mean change in heart rate, P=9.1±1.3 and 9.2±1.8, P+T=8.8±1.2 and 6.3±1.5, P+H=8.9±1.3 and 7.8±1.5, and P+T+H=5.9±1.1 and 7.7±1.5).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(P+T+H) vs reserpine 35 mg plus HCTZ 35 mg (R+T)				Withdrawals for any reason were similar between the treatment arms and were not statistically significant (R+T=14 patients, P=11, P+T=12, P+H=14, and P+T+H=16).
Stevens et al.[127] (1982) <u>Dose-finding phase:</u> Propranolol 80, 160, 240, or 320 mg/day in 2 divided doses vs propranolol and HCTZ 80-50, 160-50, 240-50, 320-50 mg/day in 2 divided doses (fixed-dose combination product) <u>Double-blind phase:</u> Propranolol and HCTZ (fixed-dose combination product) vs	DB, PG, RCT Patients with mild to moderate essential HTN (DBP 100 to 125 mm Hg)	N=158 25 weeks	Primary: Mean changes of SBP and DB, heart rate, lab values Secondary: Not reported	Primary: After the 12 week dose finding-phase, 94% of patients had a decrease ≥10 mm Hg in DBP. The mean SBP and DBP reduced from 158.0 (±17.3)/105.6 (±6.0) mm Hg to 131.5 (±14.4)/86.4 (± 6.7) mm Hg (P<0.001). After the 10 week portion of the study, there were significantly greater increases (P<0.05) in mean SBP or DBP with propranolol and HCTZ alone vs the combination product of propranolol and HCTZ from the end of the dose-finding to the last four biweekly visits to the mean of those visits, and to the last visit. The mean increases of SBP and DBP at the endpoint were: propranolol, 10.2/6.3 mm Hg; HCTZ 13.1/9.3 mm Hg; propranolol-HCTZ combination product 3/1.5 mm Hg. There was a significant decrease in heart rate as the dose of propranolol was increased thought the trial (P>0.30). The only lab value that showed a statistically significant change was serum chloride. The percent of patients that fell outside of the normal range were as follows: propranolol 6/36 (17%), HCTZ 14/37 (38%), and combination 4/28 (14%); P<0.05. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
propranolol vs HCTZ				
de Leeuw et al.[128] (1997) Verapamil SR and trandolapril 180-2 mg/day, atenolol and chlorthalidone 100-25 mg/day, or lisinopril and HCTZ 20-12.5 mg/day (fixed-dose combination products) vs placebo All patients entered a SB, placebo 4 week run in period.	DB, MC, PC, RCT Patients 18 to 70 years of age with essential HTN (WHO I or II) newly or unsuccessfully treated, with supine DBP 101 to 114 mm Hg in week 4 of the run in period	N=205 12 weeks	Primary: Changes in supine blood pressure, standing blood pressure response rates, normalization rates Secondary: Not reported	Primary: Each of the three treatments was significantly more effective than placebo in reducing seated DBP. Changes in DBP were as follows: verapamil SR and trandolapril, -13 (95% CI, -16 to -9); atenolol and chlorthalidone, -13 (95% CI, -16 to -9); lisinopril and HCTZ, -12 (95% CI, -15 to -9) and placebo, -3 (95% CI, -7 to 0) (P=0.0001 for all vs placebo), but there was not a significance among the treatments (P values not reported). Each of the three treatments was significantly more effective than placebo in reducing seated SBP. Changes in SBP were as follows: verapamil SR and trandolapril, -27 (95% CI, -33 to -21); atenolol and chlorthalidone, -28 (95% CI, -34 to -22); lisinopril and HCTZ, -23 (95% CI, -29 to -17) and placebo, -3 (95% CI, -9 to 3) (P=0.0001 for all vs placebo), but there was not a significance among the treatments (P values not reported). Effects on standing blood pressure demonstrated similar results as the effects on sitting blood pressure (P values not reported). Normalization of DBP (<90 mm Hg), corrected for placebo, were significantly higher with all treatments compared to placebo (verapamil SR and trandolapril, 33% [95% CI, 16 to 50; P<0.0005]; atenolol and chlorthalidone, 31% [95% CI, 14 to 48; P<0.002] and lisinopril and HCTZ, 25% [95% CI, 9 to 42; P<0.005]). Response rates (normalization of DBP or a reduction in DBP >10 mm Hg), corrected for placebo, were significantly higher with all treatments compared to placebo (verapamil SR and trandolapril, 40% [95% CI, 22 to 58; P<0.0001], atenolol and chlorthalidone, 44% [95% CI, 27 to 61; P<0.0001] and lisinopril and HCTZ, 37% [95% CI, 19 to 55; P<0.0002]). Secondary: Not reported

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Casas et al.[129] (2005) ACE inhibitor or ARBs compared to other antihypertensive drugs (β-adrenergic blocking agents, α-adrenergic blocking agents, calcium-channel blocking agents, or combinations) vs ACE inhibitor or ARBs compared to placebo Specific agents and doses were not specified.	MA (127 trials) Studies in adults that examined the effect of any drug treatment with a blood pressure lowering action on progression of renal disease	N=not reported 4.2 years (mean)	Primary: Doubling of serum creatinine, and ESRD Secondary: Serum creatinine, urine albumin excretion and GFR	Primary: Treatment with ACE inhibitors or ARBs resulted in a nonsignificant reduction in the risk of doubling of creatinine vs other antihypertensives (P=0.07) with no differences in the degree of change of SBP or DBP between the groups. A small reduction in ESRD was observed in patients receiving ACE inhibitors or ARBs compared to other antihypertensives (P=0.04) with no differences in the degree of change of SBP or DBP between the groups. Secondary: Small reductions in serum creatinine and in SBP were noted when ACE inhibitors or ARBs were compared to other antihypertensives (P=0.01). Small reduction in daily urinary albumin excretion in favor of ACE inhibitor or ARBs were reported when these agents were compared to other antihypertensives (P=0.001). Compared to other drugs, ACE inhibitors or ARBs had no effect on the GFR.
Baguet et al.[130] (2007) Antihypertensive drugs (enalapril, ramipril, trandolapril, candesartan, irbesartan, losartan, olmesartan, telmisartan,	MA Patients greater than 18 years of age with mild or moderate essential HTN (SBP 140 to 179 mm Hg and/or DBP 90 to 109 mm Hg)	N=10,818 8 to 12 weeks	Primary: Weighted average reductions in SBP and DBP Secondary: Not reported	Primary: Data did not reflect outcomes from direct, head-to-head comparative trials or formal comparisons between drugs. Diuretics (-19.2 mm Hg; 95% CI, -20.3 to -18.0), calcium channel blockers (-16.4 mm Hg; 95% CI, -17.0 to -15.8) and ACE inhibitors (-15.6 mm Hg; 95% CI, -17.6 to -13.6) produced the greatest reductions in SBP from baseline (P values not reported). The magnitude of DBP reductions were generally similar among all drug classes; however, the greatest reductions in DBP from baseline were observed with the β-blocker, atenolol (-11.4 mm Hg; 95% CI, -12.0 to -10.9), calcium channel blockers (-11.4 mm Hg; 95% CI, -11.8 to -11.1) and diuretics (-11.1 mm Hg; 95% CI, -11.7 to -10.5) (P values were not

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
valsartan, HCTZ, indapamide SR*, atenolol, amlodipine, lercanidipine*, manidipine*, enalapril, ramipril, trandolapril, and aliskiren) Drugs were used as monotherapy, either at a fixed daily dosage or in increasing dosages. Although cicletanine*, furosemide and spironolactone were considered for inclusion, none of the trials relating to these agents satisfied all inclusion criteria.				reported). The weighted average reduction of SBP and DBP for each drug class were as follows: Diuretics: -19.2 (95% CI, -20.3 to -18.0) and -11.1 mm Hg (95% CI, -11.7 to -10.5), respectively. β-blockers: -14.8 (95% CI, -15.9 to -13.7) and -11.4 mm Hg (95% CI, -12.0 to -10.9), respectively. Calcium channel blockers: -16.4 (95% CI, -17.0 to -15.8) and -11.4 mm Hg (95% CI, -11.8 to -11.1), respectively. ACE inhibitors: -15.6 (95% CI, -17.6 to -13.6) and -10.8 mm Hg (95% CI, -11.9 to -9.7), respectively. ARBs: -13.2 (95% CI, -13.6 to -12.9) and -10.3 mm Hg (95% CI, -10.5 to -10.1), respectively. Renin inhibitor: -13.5 (95% CI, -14.2 to -12.9) and -11.3 mm Hg (95% CI, -11.7 to -10.9), respectively. Secondary: Not reported
Post Myocardial Infarction and Other Cardiovascular Outcomes Trials				
Gottlieb et al.[131] (2001) Atenolol vs metoprolol	RETRO Patients discharged from the hospital with the diagnosis of an acute MI and on a β-blocker	N=69,338 2 years	Primary: Mortality rates at 1 and 2 year(s) Secondary: Not reported	Primary: β-blockers demonstrated a 40% overall reduction in mortality compared to those patient who did not receive β-blocker therapy. One year mortality rates in the three groups were metoprolol 8.32% (CI, 8.07 to 8.58, atenolol 8.16% (CI, 7.76 to 8.58), propranolol 9.55% (CI, 9.69 to 10.48), and other 9.19% (CI, 8.16 to 10.33). Two year mortality rates in the three groups were metoprolol 13.52% (CI,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs propranolol vs other (not specified)				13.21 to 13.84), atenolol 13.41% (CI, 12.91 to 13.93), propranolol 15.91% (CI, 14.83 to 17.05), and other 15.17% (CI, 13.88 to 16.56). There were no differences between atenolol and metoprolol at the end of the two years, both of which were statistically better than propranolol. Compared to metoprolol, patients discharged on propranolol had 15% increased mortality at one year and 18% increased mortality at two years, which were significantly higher than metoprolol. Secondary: Not reported
Testa et al.[132] (2014) Patients taking atenolol vs Patients not taking atenolol	Observational Patients aged ≥65 years with isolated HTN	N=972 12 years	Primary: Mortality Secondary: Not reported	Primary: Univariate analysis shows that elderly participants taking atenolol show greater mortality than those not taking atenolol (52.4 vs 66.7%; P=0.047). Cox regression analysis on 12-year mortality showed that age, number of diseases, number of drugs, basic activity of daily living ≥l%, and social support score were predictive; whereas female sex and Mini-Mental State Examination score were protective of long-term mortality. Additionally, pulse arterial pressure (HR, 1.02; 95% CI, 1.01 to 1.03; P=0.035) and atenolol use (HR, 1.89; 95% CI, 1.03 to 4.25; P<0.05) were predictive of long-term mortality. Secondary: Not reported
Black et al.[133] (2003) CONVINCE Atenolol 50 mg QD vs verapamil ER 180 mg QD	AC, DB, MC, RCT Patients 55 years of age and older with HTN and ≥1 risk factor for cardiovascular disease	N=16,476 3 years	Primary: Composite first occurrence of acute MI, stroke or cardiovascular disease-related death Secondary: Cardiovascular endpoints expanded, all-	Primary: There was no significant difference between the verapamil treatment group and the atenolol or HCTZ treatment groups in the composite primary endpoint (HR, 1.02; 95% CI, 0.88 to 1.18; P=0.77). Secondary: There was no significant difference between the verapamil treatment group and the atenolol or HCTZ treatment group in rates of cardiovascular-related hospitalization (P=0.31), death (all-cause mortality) (P=0.32) and cancer rates (P=0.46). Patients treated with verapamil experienced a significantly higher rate of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs HCTZ 12.5 mg QD			cause mortality, cancer, hospitalization for bleeding, incidence of primary endpoints between 6AM and noon, adverse events	death or bleeding unrelated to stroke (HR, 1.54; 95% CI, 1.15 to 2.04; P=0.003). Primary endpoints did not differ significantly based on time of day (P=0.43). Patients treated with verapamil were more likely to withdraw for adverse events or symptoms than those treated with atenolol or HCTZ (P=0.02).
Dahlöf et al.[134] (2002) LIFE Atenolol 50 to 100 mg QD vs losartan 50 to 100 mg QD HCTZ 12.5 to 25 mg QD was added if needed for blood pressure control.	DB, DD, PG, RCT Patients 55 to 80 years old with essential HTN (sitting SBP/DBP 160 to 200 to 95 to 115 mm Hg) and left ventricular hypertrophy	N=9,193 ≥4 years	Primary: Composite of cardiovascular death, MI and stroke Secondary: All-cause mortality, hospitalization for angina or heart failure, revascularization procedures, resuscitated cardiac arrest, new-onset diabetes	Primary: SBP fell by 30.2 and 29.1 mm Hg in the losartan and atenolol groups, respectively (treatment difference, P=0.017) and DBP fell by 16.6 and 16.8 mm Hg, respectively (treatment difference, P=0.37). MAP was 102.2 and 102.4 mm Hg, respectively (P value not significant). Heart rate decreased more in patients assigned to atenolol than losartan (-7.7 vs -1.8 beats/minute, respectively; P<0.0001). Compared to atenolol, the primary composite occurred in 13.0% fewer patients receiving losartan (RR, 0.87; 95% CI, 0.77 to 0.98; P=0.021). While there was no difference in the incidence cardiovascular mortality (P=0.206) and MI (P=0.491), losartan treatment resulted in a 24.9% relative risk reduction in stroke compared to atenolol (P=0.001). Secondary: A 25% lower incidence of new-onset diabetes was reported with losartan compared to atenolol (P=0.001). There was no significant difference among the other secondary end points between the two treatment groups. Note: At end point or end of follow-up, 18 and 26% of patients on losartan were receiving HCTZ alone or with other drugs, respectively. In the atenolol group, 16 and 22% of patients were receiving HCTZ alone or with other drugs, respectively.
Julius et al.[135] (2004) LIFE Black Subset Atenolol 50 to 100	Post hoc analysis Patients 55 to 80 years old with essential HTN	N=523 ≥4 years	Primary: Composite of cardiovascular death, MI and stroke	Primary: Compared to atenolol (11.2%), losartan in the United States African American population resulted in a greater incidence of the composite end point (17.4%; P=0.033).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg QD vs losartan 50 to 100 mg QD HCTZ 12.5 to 25 mg QD was added if needed for blood pressure control.	(sitting SBP/DBP 160 to 200/95 to 115 mm Hg) and left ventricular hypertrophy		Secondary: Not reported	HRs favored atenolol across all parameters (P=0.246 for cardiovascular mortality, P=0.140 for MI, and P=0.030 for stroke). In African American patients, blood pressure reduction was similar in both groups, and regression of electrocardiographic-left ventricular hypertrophy was greater with losartan. Secondary: Not reported
Lindholm et al.[136] (2002) LIFE Diabetic Subset Atenolol 50 to 100 mg QD vs losartan 50 to 100 mg QD HCTZ 12.5 to 25 mg QD was added if needed for blood pressure control.	Post hoc analysis Patients 55 to 80 years old with essential HTN (sitting SBP/DBP 160 to 200/95 to 115 mm Hg) and left ventricular hypertrophy	N=1,195 ≥4 years	Primary: Composite of cardiovascular death, MI and stroke Secondary: All-cause mortality	Primary: Compared to atenolol, losartan resulted in a 24% decrease in the primary composite end point (P=0.031). Losartan treatment resulted in a 37% risk reduction in cardiovascular deaths vs atenolol (P=0.028). Losartan treatment resulted in a 39% risk reduction in all-cause mortality vs atenolol (P=0.002). Mean blood pressure fell to 146/79 mm Hg in losartan patients and 148/79 mm Hg in atenolol patients. Secondary: Mortality from all causes was 63 and 104 in the losartan and atenolol groups, respectively (RR, 0.61; P=0.002).
Kjeldsen et al.[137] (2002) LIFE Isolated Systolic Hypertension Subset Atenolol 50 to 100 mg QD	Post hoc analysis Patients 55 to 80 years old with isolated systolic HTN (SBP of 160 to 200 mm Hg and DBP <90 mm Hg) and left ventricular	N=1,326 ≥4 years	Primary: Composite of cardiovascular death, MI, or stroke Secondary: All-cause mortality	Primary: Compared to atenolol, losartan resulted in a trend towards a 25% reduction in the primary end point (P=0.06). Losartan treatment resulted in a 46% risk reduction in cardiovascular mortality (P=0.01) and 40% risk reduction in stroke compared to atenolol (P=0.02). There was no difference in the incidence of MI. Blood pressure was reduced by 28/9 and 28/9 mm Hg in the losartan and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs losartan 50 to 100 mg QD HCTZ 12.5 to 25 mg QD was added if needed for blood pressure control.	hypertrophy			atenolol arms. Secondary: Patients receiving losartan also had reductions in all-cause mortality (28%; P<0.046).
Fossum et al.[138] (2006) ICARUS, a LIFE substudy Atenolol 50 to 100 mg QD vs losartan 50 to 100 mg QD All patients received HCTZ 12.5 to 25 mg/day if need for blood pressure control.	DB, DD, PG, RCT Patients 55 to 80 years old with essential HTN (sitting SBP/DBP 160 to 200/95 to 115 mm Hg) and left ventricular hypertrophy	N=81 3 years	Primary: Amount and density of atherosclerotic lesions in the common carotid arteries and carotid bulb Secondary: Not reported	Primary: The amount of plaque decreased in the losartan group and increased in the atenolol group, though the difference between groups was not statistically significant (P=0.471). Patients in the atenolol group had a greater increase in plaque index compared to the losartan group, though the difference between groups was not statistically significant (P=0.742) Secondary: Not reported
Kizer et al.[139] (2005) (LIFE substudy) Atenolol 50 to 100 mg QD vs	DB, DD, PG, RCT Patients 55 to 80 years old with essential HTN (sitting SBP/DBP 160 to 200/95 to 115 mm Hg) and left ventricular	N=9,193 ≥4 years	Primary: Reduction in the risk of different stroke subtypes and neurological deficits Secondary: Not reported	Primary: The risk of fatal stroke was significantly decreased in the losartan group compared to the atenolol group (P=0.032). The risk of atherothrombotic stroke was significantly decreased in the losartan group compared to the atenolol group (P=0.001). Comparable risk reductions were observed for hemorrhagic and embolic stroke but did not reach statistical significance.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
losartan 50 to 100 mg QD All patients received HCTZ 12.5 to 25 mg/day if need for blood pressure control.	hypertrophy			The risk of recurrent stroke was significantly reduced in the losartan arm compared to the atenolol arm (P=0.017). The number of neurological deficits per stroke was similar (P=0.68), but there were fewer strokes in the losartan group for nearly every level of stroke severity. Secondary: Not reported
Wachtell et al.[140] (2005) (LIFE substudy) Atenolol 50 to 100 mg QD vs losartan 50 to 100 mg QD All patients received HCTZ 12.5 to 25 mg/day if need for blood pressure control.	DB, DD, PG, RCT Patients 55 to 80 years old with essential HTN (sitting SBP/DBP 160 to 200/95 to 115 mm Hg) and left ventricular hypertrophy	N=8,851 (patients in LIFE with no baseline history of AF but at risk for AF) ≥4 years	Primary: Incidence of new-onset AF and outcome Secondary: Not reported	Primary: Significantly fewer patients in the losartan group experienced new-onset AF compared to the atenolol group (P<0.001). Randomization to losartan treatment was associated with a 33% lower rate of new onset AF independent of other risk factors (P<0.001). Patients in the losartan group had a 40% lower rate of composite events consisting of cardiovascular death, fatal or non-fatal stroke, and fatal or non-fatal MI (P=0.03). Significantly fewer strokes occurred in the losartan group compared to the atenolol group (P=0.01), and there was a trend toward fewer MIs in the losartan group (P=0.16). There was no significant difference in cardiovascular mortality between groups. In contrast, the atenolol group experienced significantly fewer hospitalizations for heart failure (P=0.004) and a trend toward fewer sudden cardiac deaths (P=0.07). Secondary: Not reported
Wachtell et al.[141] (2005) (LIFE substudy)	DB, DD, PG, RCT Patients 55 to 80	N=342 (LIFE patients with AF at the	Primary: Cardiovascular morbidity and	Primary: Patients with a history of AF had significantly higher rates of cardiovascular and all-cause mortality, fatal and non-fatal stroke, heart

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Atenolol 50 to 100 mg QD vs losartan 50 to 100 mg QD All patients received HCTZ 12.5 to 25 mg/day if need for blood pressure control.	years old with essential HTN (sitting SBP/DBP 160 to 200/95 to115 mm Hg) and left ventricular hypertrophy	start of the LIFE study) ≥4 years	mortality Secondary: Not reported	failure, revascularization and sudden cardiac death compared to patients without AF (P<0.001). Patients with a history of AF had similar rates of MI and hospitalization for angina pectoris (P≥0.209). The primary composite endpoint of cardiovascular mortality, stroke and MI occurred in significantly fewer patients in the losartan group compared to the atenolol group (P=0.009). The difference in MI between groups was not significant. Treatment with losartan trended toward lower all-cause mortality (P=0.09) and fewer pacemaker implantations (P=0.065). Secondary: Not reported
Dahlöf et al.[142] (1991) Hypertension (STOP) Atenolol 50 mg QD, HCTZ 25 mg QD plus amiloride 2.5 mg QD, metoprolol 100 mg QD, or pindolol 5 mg QD vs placebo	DB, MC, RCT Swedish men and women 70 to 84 years old with treated or untreated essential HTN defined as SBP ≥180 mm Hg with a DBP of ≥90 mm Hg, or DBP >105 mm Hg irrespective of the SBP measured on 3 separate occasions during a 1-month placebo run-in phase in previously untreated patients	N=1,627 25 months	Primary: Frequency of stroke, MI, and other cardiovascular death Secondary: Not reported	Primary: The active treatments significantly reduced the number of all primary endpoints (94 vs 58; RR, 0.60; 95% CI, 0.43 to 0.85; P=0.0031), frequency of stroke (53 vs 29; RR, 0.53; 95% CI, 0.33 to 0.86; P=0.0081) and frequency of other cardiovascular deaths (13 vs 4; RR, 0.30; 95% CI, 0.07 to 0.97) compared to placebo. There was not a statistically significant decrease observed in the rate of MI between the active treatments and placebo (28 vs 25; RR, 0.87; 95% CI, 0.49 to 1.56). Secondary: Not reported
Hannson et al.[143]	BE, MC, OL, RCT	N=6,614	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1999) HYPERTENSION -2 (STOP) <u>Conventional drug group</u> Atenolol 50 mg QD, HCTZ 25 mg QD plus amiloride 2.5 mg QD, metoprolol 100 mg QD, or pindolol 5 mg QD vs <u>Newer drug group</u> ACE inhibitors (enalapril 10 mg QD or lisinopril 10 mg QD) or calcium channel blockers (felodipine 2.5 mg QD, or isradipine 2 to 5 mg QD)	Swedish men and women between 70 to 84 years old with treated or untreated essential with HTN on 3 separate occasions defined by SBP ≥180 mm Hg, DBP >105 mm Hg, or both	60 months	Combined fatal stroke, MI, and other fatal cardiovascular disease; combined fatal and nonfatal stroke, MI, and other cardiovascular Mortality Secondary: Not reported	The combined fatal mortality endpoints occurred in 221of the 2,213 patients in the conventional drugs group and in 438 of 4,401 in the newer drugs group (RR, 0.99; 95% CI, 0.84 to 1.16; P=0.89). The combined fatal and nonfatal mortality endpoints occurred in 460 patients taking conventional drugs and in 887 taking newer drugs (RR, 0.96; 95% CI, 0.86 to 1.08; P=0.49). Secondary: Not reported
Dalhof et al.[144] (2005) ASCOT-BPLA Atenolol 50 to 100 mg/day adding bendro-flumethiazide* 1.25 to 2.5 mg/day and potassium as needed	MC, OL, RCT Patients 40 to 79 years of age with HTN and ≥3 other cardiovascular risk factors (left ventricular hypertrophy, other specified abnormalities on	N=19,257 5.5 years	Primary: Nonfatal MI (including silent MI) and fatal CHD Secondary: All-cause mortality, total stroke, primary end points minus silent MI, all coronary	Primary: No statistically significant difference in nonfatal MI and fatal CHD was reported between the amlodipine plus perindopril group compared to the atenolol plus bendroflumethiazide groups (HR, 0.90; 95% CI, 0.79 to 12; P=0.1052). Secondary: Significantly greater reductions in the following secondary end points were observed with amlodipine plus perindopril compared to atenolol plus bendroflumethiazide: all- cause mortality (P=0.0247), total stroke (P=0.0003), primary end points minus silent MI (P=0.0458), all coronary

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs amlodipine 5 to 10 mg/day adding perindopril 4 to 8 mg/day as needed If blood pressure was still not achieved, doxazosin 4 to 8 mg/day was added to the regimen.	ECG, type 2 diabetes, PAD, history of stroke or TIA, male, age ≥55 years, microalbuminuria or proteinuria, smoking, TC:HDL-C ratio ≥6, or family history of CHD)		events, total cardiovascular events and procedures, cardiovascular mortality, nonfatal and fatal heart failure, effects on primary end point and on total cardiovascular events and procedures among prespecified subgroups Tertiary: Silent MI, unstable angina, chronic stable angina, PAD, life-threatening arrhythmias, development of diabetes, development of renal impairment	events (P=0.0070), total cardiovascular events and procedures (P<0.0001), and cardiovascular mortality (P=0.0010). There were no significant differences in nonfatal and fatal heart failure between the two treatment groups (P=0.1257). The study was terminated early due to higher mortality and worse outcomes on several secondary end points observed in the atenolol study group. Tertiary: Significantly greater reductions in the following end points were observed with amlodipine plus perindopril compared to atenolol plus bendroflumethiazide: unstable angina (P=0.0115), PAD (P=0.0001), development of diabetes (P<0.0001), and development of renal impairment (P=0.0187). There were no significant differences in the incidence of silent MI (P=0.3089), chronic stable angina (P=0.8323) or life-threatening arrhythmias (P=0.8009) between the two treatment groups. There was no significant difference in the percent of patients who stopped therapy because of an adverse event between the two treatment groups (overall 25%). There was, however, a significant difference in favor of amlodipine plus perindopril in the proportion of patients who stopped trial therapy because of a serious adverse events (2 vs 3%; P<0.0001).
Pepine et al.[145] (2003) INVEST Atenolol 50 mg/day (step 1), then add HCTZ if needed (step 2), then increase doses of both (step 3),	MC, OL, RCT Patients with essential HTN	N=22,576 24 months	Primary: First occurrence of death (all cause), nonfatal MI or stroke Secondary: Cardiovascular death, angina, cardiovascular	Primary: At 24 months, in the calcium antagonist strategy subgroup, 81.5% of patients were taking verapamil SR, 62.9% trandolapril, and 43.7% HCTZ. In the non-calcium antagonist strategy, 77.5% of patients were taking atenolol, 60.3% HCTZ, and 52.4% trandolapril. After a follow-up of 61,835 patient-years (mean, 2.7 years per patient), 2,269 patients had a primary outcome event with no statistically significant difference between treatment strategies (9.93% in calcium antagonist strategy vs 10.17% in non-calcium antagonist strategy; RR,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
then add trandolapril (step 4) (non-calcium antagonist strategy) vs verapamil SR 240 mg/day (step 1), then add trandolapril if needed (step 2), then increase doses of both (step 3), then add HCTZ (step 4) (calcium antagonist strategy) Trandolapril was recommended for all patients with heart failure, diabetes, or renal insufficiency.			hospitalization, angina, blood pressure control (SBP/DBP <140/90 mm Hg or <130/85 mm Hg if diabetic or renal impairment), safety	0.98; 95% CI, 0.90 to 16; P=0.57). Secondary: There was no significant difference in the rate of cardiovascular death (P=0.94) or cardiovascular hospitalization (P=0.59) between the two treatment groups. At 24 months, angina episodes decreased in both groups, but the mean frequency was lower in the calcium antagonist strategy group (0.77 episodes/week) compared to the non-calcium antagonist strategy group (0.88 episodes/week; P=0.02). Two-year blood pressure control was similar between groups. The blood pressure goals were achieved by 65.0% (systolic) and 88.5% (diastolic) of calcium antagonist strategy patients and 64.0% (systolic) and 88.1% (diastolic) of non-calcium antagonist strategy patients. A total of 71.7% of calcium antagonist strategy patients and 70.7% of non-calcium antagonist strategy patients achieved an SBP <140 mm Hg and DBP <90 mm Hg. Both regimens were generally well tolerated. Patients in the calcium antagonist strategy group reported constipation and cough more frequently than patients in the non-calcium antagonist strategy group, while non-calcium antagonist strategy patients experienced more dyspnea, lightheadedness, symptomatic bradycardia and wheezing (all were statistically significant with P≤0.05).
Mancia et al.[146] (2007) INVEST Atenolol 25 to 200 mg QD vs verapamil SR 120 to 480 mg QD	MC, open blinded endpoint, PRO, RCT Patients with HTN, requiring drug therapy (BP>140/90 or >130/80 mm Hg if diabetic or with renal impairment), and CAD	N=22,576 24 months	Primary: Occurrence of death, nonfatal MI and nonfatal stroke Secondary: Blood pressure control rates	Primary: Rates (death, nonfatal MI and nonfatal stroke) were similar for both treatment groups (P value not reported). Secondary: Rates of death, MI and stoke declined as the number of office visits for which blood pressure was controlled increased (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Bangalore et al.[147] (2008) INVEST Verapamil SR 120 to 480 mg QD vs atenolol 25 to 200 mg QD Trandolapril and/or HCTZ were added to control blood pressure.	INVEST substudy Patients 50 years of age and older with hypertension requiring drug therapy (blood pressure >140/90 or >130/80 mm Hg if diabetic or with renal impairment), and documented coronary artery disease	N=22,576 24 months	Primary: First occurrence of death, nonfatal MI, nonfatal stroke Secondary: Death, total MI, total stroke	Primary: No significant difference was observed between groups in the primary endpoint (P=0.30). Among patients with the primary outcome, no significant difference was observed between groups in the risk of death (P=0.94). There was no significant difference between groups in the risk of nonfatal MI (P=0.41). There was a trend toward a 29% reduction in the risk of nonfatal stroke in the verapamil group compared to the atenolol group (P=0.06). Secondary: The risks of fatal and nonfatal MI were similar between groups. No significant differences were observed between groups in fatal and nonfatal stroke (P=0.18).o
Iliuta et al.[148] (2009) Betaxolol 20 mg/day vs metoprolol 100 mg BID	OL, MC Patients who were admitted for CABG surgery	N=1352 30 days	Primary: Mortality, in-hospital occurrence of AF, total hospital stay and immobilization (days) Secondary: Not reported	Primary: Betaxolol significantly decreased 30 day mortality (P=0.001) and in-hospital AF (P=0.0001) compared to metoprolol. Patients taking betaxolol were less likely to be hospitalized for >15 days (9.94 vs 13.27, P=0.01) or immobilized for >3 days (5.19 vs 8.26, p=0.002) compared to metoprolol. Secondary: Not reported
Jonsson et al.[149] (2005) Carvedilol 6.25 to 25 mg BID vs atenolol 12.5 to 50	OL, RCT Patients between 18 to 80 years of age with chest pain consistent with an acute MI, admitted to the hospital 24 hours after onset	N=232 1.5±1.3 years	Primary: Change in global or regional LVEF after 12 months, cardiovascular endpoints, adverse events Secondary:	Primary: At baseline, mean global LVEF was 54.8% in the carvedilol and 53.0% in the atenolol group and increased after 12 months to 57.1% in the carvedilol and 56.0% in the atenolol group. There was not a significant difference between treatment groups for change in global or regional LVEF (values were not reported). There was not a significant difference in the rates of occurrence of the first serious cardiovascular events observed between the carvedilol and

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mg BID	and a confirmed diagnosis with significant increase in cardiac enzymes		Not reported	atenolol groups after adjustment for diuretic use (0.247 vs 0.299; RR, 0.83; 95% CI, 0.56 to 1.23; P=0.39). Of the nonserious adverse events reported, a greater incidence of colds hand and feet were reported in the atenolol group (38 [33.3%]) compared to the carvedilol group (24 [20%]; P=0.025). Secondary: Not reported
Pasternak et al.[150] (2014) Carvedilol vs metoprolol succinate	RETRO Danish patients aged 50 to 84 years with HF and LVEF ≤40% who received carvedilol or metoprolol succinate treatment	N=11,664 Up to 3 years (Median 2.4)	Primary: All-cause mortality Secondary: Cardiovascular mortality	Primary: The cumulative incidence of all-cause mortality was 18.3 and 18.8% in the carvedilol and metoprolol groups, respectively. After adjustment for propensity score, the risk of mortality did not differ significantly between carvedilol and metoprolol users (aHR, 0.99; 95% CI, 0.88 to 1.11). Secondary: The risk of cardiovascular mortality was not significantly different between carvedilol and metoprolol users (aHR, 1.05; 95% CI, 0.88 to 1.26).
Seo et al.[151] (2015) Carvedilol vs β1-selective β blockers (bisoprolol, metoprolol, and nebivolol)	PRO, propensity-score matched cohort Patients ≥18 years of age with acute MI undergoing percutaneous coronary intervention	N=7,863 mean follow-up of 243 ± 144 days	Primary: All-cause death or MI during follow-up Secondary: All-cause death, cardiac death, and MI	Primary: Of the 7,863 patients examined, 6,231 (79.2%) were treated with carvedilol and 1,632 (20.7%) were treated with β1-selective β -blockers. During the follow-up period, the primary end point of all-cause death or MI occurred in 94 patients (1.5%) in the carvedilol group and 31 patients (1.9%) in the β1-selective β -blockers group. In the multivariate Cox regression model, no differences in the risk of all-cause death or MI were observed between the carvedilol and β1-selective β –blocker groups. Secondary: The risks of all-cause death, cardiac death, and MI were also similar between the carvedilol and β1-selective β –blocker groups during the follow-up period.
Olsson et al.[152] (1992) Metoprolol 100 mg BID	MA (5 trials) Patients with a past history of MI	N=5,474 3 months to 3 years	Primary: All-cause mortality, sudden deaths	Primary: Metoprolol significantly reduced all-cause mortality compared to placebo (188 vs 223 deaths; P=0.036). Metoprolol significantly reduced sudden deaths compared to placebo (62

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo			Secondary: Not reported	vs 104 deaths; P=0.002). Secondary: Not reported
Piccini et al.[153] (2014) Amiodarone vs sotalol vs no antiarrhythmic drug (AAD)	RETRO Patients with CAD and AF	N=2,838 Median follow-up 4.2 years	Primary: All-cause mortality Secondary: Not reported	Primary: In unadjusted and adjusted settings, mortality rates were lower in patients treated with sotalol compared with amiodarone or no AAD. After adjustment for baseline characteristics only, the 1-year mortality rate was 10% in those treated with sotalol, 20% in those treated with amiodarone, and 14% in those treated with no AAD (no P-value reported). Landmark analysis at 60 days and one year was also performed. After adjustment and weighting, sotalol was associated with improved survival from 0 to 60 days compared with amiodarone (HR, 0.14; 95% CI, 0.06 to 0.32) but not at later time points (≥60 days or ≥1 year). Similarly, compared with no AAD therapy, sotalol was not associated with improved survival beyond 60 days. Cumulative survival after one year in patients treated with sotalol vs no AAD was also not improved (P=0.64). Secondary: Not reported
No authors listed[154] (abstract) (1983) Timolol vs placebo	DB, MC, PC, RCT Patients <75 years of age surviving an acute MI	N=1,884 12 to 33 months	Primary: All-cause mortality Secondary: Not reported	Primary: Long term treatment with timolol improved prognosis. A significant difference in life table mortality of 39.3% between treatments was observed (13.3 vs 21.9%; P=0.0003). The difference was due to a lower rate of sudden cardiac death with timolol compared to placebo (7.7 vs 13.9%; P=0.0001). Secondary: Not reported
Patel et al.[155] (2014) β-blocker therapy (carvedilol, metoprolol	RETRO Medicare patients in the OPTIMIZE-HF registry (having a primary discharge	N=2,198 (1099 propensity-matched pairs) Up to 6 years	Primary: composite endpoint of all-cause mortality or HF rehospitalization	Primary: Discharge prescriptions for β-blockers to older HF with preserved ejection fraction patients who were not receiving these drugs prior to admission had no association with the primary composite endpoint during a median of 2.2 years of follow-up (HR, 1.03; 95% CI, 0.94 to 1.13; P=0.569). This association was homogeneous across various clinically relevant

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
succinate, and bisoprolol at their respective guideline-recommended target doses of 50, 200, and 10 mg/day) vs no β-blocker therapy	diagnosis of HF), aged ≥65 years with EF ≥40% who were eligible for new discharge prescriptions of β-blockers	(Median 2.2)	Secondary: All-cause mortality, HF rehospitalization, and all-cause rehospitalization	subgroups. Secondary: HRs for all-cause mortality and HF rehospitalization associated with a prescription for initiation of β-blocker therapy were 0.99 (95% CI, 0.90 to 1.10; P=0.897) and 1.17 (95% CI, 1.03 to 1.34; P=0.014), respectively. The latter association lost significance when higher EF cutoffs of ≥45%, ≥50% and ≥55% were used.
Hannson et al.[156] (2000) NORDIL Conventional therapy (diuretic, β-blocker or both) vs diltiazem 180 to 360 mg QD	BE, MC, OL, PRO, RCT Patients 50 to 74 years of age with DBP ≥100 mm Hg and previously untreated	N=10,881 4.5 years	Primary: Combined fatal and nonfatal stroke, fatal and nonfatal MI, other cardiovascular death Secondary: Fatal plus nonfatal stroke and fatal plus nonfatal MI	Primary: The primary endpoint occurred in 403 of the diltiazem patients and 400 of the diuretic/β-blocker patients (RR, 1.00; 95% CI, 0.87 to 1.15; P=0.97). Secondary: Rates of secondary endpoints were similar between the groups. Fatal plus nonfatal stroke occurred in 159 of the diltiazem patients and 196 of the diuretic/β-blocker patients (P=0.04). Fatal plus nonfatal MI occurred in 183 of the diltiazem patients and 157 of the diuretic/β-blocker patients (P=0.17). Other endpoints were not statistically different between the groups including cardiovascular death (P=0.41), all cardiac events (P=0.57) and congestive heart failure (P=0.42).
Messerli et al.[157] (1998) β-blockers (atenolol, metoprolol or pindolol) vs	MA 10 RCTs lasting ≥1 year, which used as first line agents diuretics and/or β-blockers and reported morbidity and	N=16,164 1 year	Primary: Cardiovascular morbidity and mortality, all-cause morbidity Secondary: Not reported	Primary: Diuretic treatment significantly reduced the odds for cardiovascular mortality by 25% (OR, 0.75; 95% CI, 0.64 to 0.87), while β-blockers did not reduce cardiovascular mortality (OR, 0.98; 95% CI, 0.78 to 1.23; P values not reported). Diuretic treatment significantly reduced the odds for all-cause mortality by 14% (OR, 0.86; 95% CI, 0.77 to 0.96), while β-blockers did not reduce all-cause mortality (OR, 1.05; 95% CI, 0.88 to 1.25; P values not

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
diuretics (amiloride, chlorthalidone, HCTZ, HCTZ and triamterene [fixed-dose combination product], or thiazide)	mortality outcomes in patients ≥60 years of age with HTN			reported). Secondary: Not reported
Wiysonge et al.[158] (2007) β-blockers (atenolol, metoprolol, oxprenolol*, or propranolol) vs other antihypertensive therapies (i.e., placebo, diuretics, calcium channel blockers, or renin-angiotensin system inhibitors)	MA 13 RCTs evaluating patients ≥18 years of age with HTN	N=91,561 Duration varied	Primary: All-cause mortality Secondary: Stroke, CHD, cardiovascular death, total cardiovascular disease, adverse reactions	Primary: There was not a significant difference observed in all-cause mortality between β-blocker therapy and placebo (RR, 0.99; 95% CI, 0.88 to 1.11; P value not reported), diuretics (RR, 1.04; 95% CI, 0.91 to 1.19; P value not reported) or renin-angiotensin system inhibitors (RR, 1.10; 95% CI, 0.98 to 1.24; P value not reported). There was a significantly higher rate in all-cause mortality with β-blocker therapy compared to calcium channel blockers (RR, 1.07; 95% CI, 1.00 to 1.14; P=0.04). Secondary: There was a significant decrease in stroke observed with β-blocker therapy compared to placebo (RR, 0.80; 95% CI, 0.66 to 0.96). Also there was a significant increase in stroke with β-blocker therapy compared to calcium channel blockers (RR, 1.24; 95% CI, 1.11 to 1.40) and renin-angiotensin system inhibitors (RR, 1.30; 95% CI, 1.11 to 1.53), but there was no difference observed compared to diuretics (RR, 1.17; 95% CI, 0.65 to 2.09). CHD risk was not significantly different between β-blocker therapy and placebo (RR, 0.93; 95% CI, 0.81 to 1.07]), diuretics (RR, 1.12; 95% CI, 0.82 to 1.54), calcium channel blockers (RR, 1.05; 95% CI, 0.96 to 1.15) or renin-angiotensin system inhibitors (RR, 0.90; 95% CI, 0.76 to 1.06). The risk of total cardiovascular disease was lower with β-blocker therapy compared to placebo (RR, 0.88; 95% CI, 0.79 to 0.97). The effect of β-blocker therapy on cardiovascular disease was significantly worse than that of calcium channel blockers (RR, 1.18; 95% CI, 1.08 to 1.29), but was not significantly different from that of diuretics (RR, 1.13; 95% CI, 0.99 to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				1.28) or renin-angiotensin system inhibitors (RR, 1.00; 95% CI, 0.72 to 1.3). There was a significantly higher rate of discontinuation due to side effects with β-blocker therapy compared to diuretics (RR, 1.86; 95% CI, 1.39 to 2.50) and renin-angiotensin system inhibitors (RR, 1.41; 95% CI, 1.29 to 1.54), but there was no significant difference compared to calcium channel blockers (RR, 1.20; 95% CI, 0.71 to 2.04). Actual side effects were not reported.
Lindholm et al.[159] (2005) β-blocker therapy (atenolol, metoprolol, oxprenolol*, pindolol, or propranolol) vs other antihypertensive therapies (amiloride, amlodipine, bendro-flumethiazide*, captopril, diltiazem, enalapril, felodipine, HCTZ, isradipine, lacidipine, lisinopril, losartan, or verapamil)	MA 13 RCTs evaluating the treatment of primary HTN with a β-blocker as first-line treatment (in ≥50% of all patients in one treatment group) and outcome data for all-cause mortality, cardiovascular morbidity or both	N=105,951 2.1 to 10.0 years	Primary: Stroke, MI, all-cause mortality Secondary: Not reported	Primary: The RR of stroke was 16% higher with β-blocker therapy than for the comparator therapies (RR, 1.16; 95% CI, 1.04 to 1.30; P=0.009). The RR of stroke was the highest with atenolol (26% higher) compared to other non β-blockers (RR, 1.26%; 95% CI, 15 to 38; P<0.0001). The relative risk of MI was 2% higher for β- blocker therapy than for the comparator therapies (RR, 1.02; 95% CI, 0.93 to 1.12), which was not significant (P value not reported). The RR of all-cause mortality was 3% higher for β-blocker therapy than for the comparator therapies (RR, 1.16; 95% CI, 0.99 to 1.08; P=0.14). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
or placebo				
Freemantle et al.[160] (1999) β-blockers (acebutolol, alprenolol, atenolol, betaxolol, carvedilol, labetalol, oxprenolol*, pindolol, practolol*, propranolol, sotalol, timolol and xamoterol*) vs control (agents were not specified)	MA (82 trials) Patients with acute or past MI	N=54,234 6 to 48 months	Primary: All-cause mortality Secondary: Nonfatal reinfarction and withdrawal from treatment	Primary: The pooled random effects in short term trials demonstrated a mortality rate of 10.5% (3,062 out of 29,260 patients) which is a 4% reduction compared to the controlled groups (OR, 0.96; 95% CI, 0.85 to 1.08). The pooled random effects in long term trials demonstrated a mortality rate of 9.7% (2415 out of 24974 patients) which is 23% reduction when compared to the controlled groups (OR, 0.77; 95% CI, 0.69 to 0.85). Individually, only four drugs achieved a statistically significant reduction in the death: propranolol (OR, 0.71; CI, 0.59 to 0.85]), timolol (OR, 0.59; CI, 0.46 to 0.77), metoprolol (OR, 0.80; CI, 0.66 to 0.96; and acebutolol (OR, 0.49; CI, 0.25 to 0.93). Secondary: A reduction in nonfatal re-infarctions of 0.9 events in every 100 (0.3 to 1.6) annually is suggested by this analysis; therefore about 107 patients would require treatment for one year to avoid one nonfatal reinfarction. Overall, 5,151 of 21,954 patients (23.5%) withdrew from treatment. with withdrawal occurring more often in the β-blocker groups. When comparing to placebo, the difference in annualized rate of withdrawal was 1.16 in 100 patients treated (1.16; 95% CI, 0.56 to 1.76).
Miscellaneous				
Schellenburg et al.[161] (2008) Metoprolol 47.5 to 142.5 mg/day vs nebivolol 5	DB, PRO, RCT Patients 18 to 65 years of age with the diagnosis of migraine with/ without aura, ≥1 year history, onset prior to 50 years of age, written record	N=38 30 weeks	Primary: Number of migraine attacks Secondary: Onset of action, duration of attacks, responder rate, severity, use of pain medication,	Primary: There was not a significant difference in the frequency of migraine attacks observed between metoprolol and nebivolol (1.3±1.0 vs 1.6±1.5, respectively; P value not reported). Secondary: There was not a significant difference in any of the secondary endpoints observed between metoprolol and nebivolol (P values not reported). Use of acute pain medication decreased with both treatments, as well as

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day	of attacks for the previous 3 months and ≥2 attack/month during screening		migraine disability assessment, QOL score	accompanying symptoms. Both patient and physician evaluations of disability and disease status were similarly favorable to the two treatments (P values not reported).
Silberstein et al.[162] (2011) Propranolol ER 240 mg/day vs placebo	DB, MC, PC, RCT Patients with chronic migraine inadequately controlled (≥10 headaches/month) with topiramate (50 to 100 mg/day)	N=191 6 months	Primary: 28 day moderate to severe headache rate reduction at six months (weeks 16 to 24) compared to baseline (weeks -4 to 0) Secondary: Not reported	Primary: The six month reduction in moderate to severe 28 day headache rate and total 28 day headache rate for combination therapy vs topiramate was not significantly different (4.0 vs 4.5 days; P=0.57 and 6.2 vs 6.1; P=0.91). Secondary: Not reported
Tfelt-Hansen et al.[163] (1984) Timolol 10 mg BID vs propranolol 80 mg BID vs placebo All patients entered a 4 week pretreatment period.	DB, PC, RCT, XO Patients 18 to 65 years of age with a history of 2 to 6 common migraine attacks per month	N=96 40 weeks	Primary: Frequency, duration and severity of attacks; number of responders (≥50% reduction in the frequency of attacks compared to baseline) Secondary: Frequency of attacks with associated symptoms, frequency of attacks requiring relief medication	Primary: Both timolol and propranolol decreased the frequency of attacks from baseline (P<0.01 for both). For severity of headache attacks, a small but significant reduction was observed with timolol (P<0.05 vs baseline). There was no effect on duration of attacks with either timolol or propranolol. The number of responders was significantly higher with timolol (n=44) and propranolol (n=48) compared to placebo (n=24; P<0.01 for both). Secondary: Both timolol and propranolol decreased the frequency of attacks associated with nausea or frequency of attacks associated with symptomatic therapy (P<0.01 for both vs baseline).
Linde et al.[164] (2004)	MA	N=5,072	Primary: Headache and	Primary: Compared to placebo, propranolol showed a significant advantage in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Propranolol 60 to 320 mg/day vs placebo or another agent (calcium channel blockers, other β-blockers or other agent)	26 randomized and quasi-randomized clinical trials of ≥4 weeks duration comparing clinical effects of propranolol with placebo or another drug in adult patients with migraine	4 to 30 weeks	migraine frequency Secondary: Not reported	response to treatment with overall RR of response (“responder ratio”) of 1.94 (95% CI, 1.61 to 2.35). Compared to placebo, propranolol showed a significant advantage for the reduction of frequency of migraines with overall mean difference of -0.40 (95% CI, -0.56 to -0.24). Propranolol did not demonstrate a significantly greater response to treatment compared to calcium channel blockers with an overall responder ratio of 1.00 (95% CI, 0.92 to 1.09). Propranolol did not demonstrate a significantly greater reduction in migraine frequency compared to calcium channel blockers with an overall mean difference of -0.02 (95% CI, 0.12 to 0.08). In the three trials comparing propranolol and nadolol, the overall responder ratio favored nadolol (responder ratio, 0.60; 95% CI, 0.37 to 0.97), but the results of the three trials were contradictory. In the three trials comparing propranolol and metoprolol, there was not a significant difference observed in the overall responder ratio between the two treatments (responder ratio, 0.78; 95% CI, 0.56 to 1.09). Propranolol did not demonstrate a significantly greater reduction in migraine frequency compared to other β-blockers with an overall mean difference of -0.01 (95% CI, 0.24 to 0.22). A quantitative MA was not performed on trials comparing propranolol to other drugs due to the great variety of comparator drugs used. One trial was significantly in favor of propranolol (vs amitriptyline), five with a trend in favor of propranolol, 11 showing no difference, two with a trend in favor of the comparator drug and one not interpretable; one of the two comparisons of propranolol alone and propranolol in combination with amitriptyline was classified as no difference, and the other as showing a trend in favor of the combination (P values not reported). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Léauté-Labrèze et al.[165] (2015) Propranolol (1 or 3 mg/kg/day, divided into two daily doses) vs placebo BID	DB, PC, RCT Patients 35 to 150 days of age with a proliferating infantile hemangioma requiring systemic therapy	N=460 24 to 96 weeks	Primary: Success (complete or nearly complete resolution of the target hemangioma) or failure of trial treatment at week 24 versus baseline according to centralized evaluation Secondary: Success or failure of trial treatment according to on-site assessments by the investigator at week 48 versus baseline	Primary: At the time of the interim analysis (188 patients completing 24 weeks of therapy), 2 of 25 patients (8%) receiving placebo had successful treatment at week 24, as compared with 4 of 41 patients (10%) receiving 1 mg/kg/day of propranolol for 3 months, 3 of 39 patients (8%) receiving 3 mg/kg/day for 3 months, 15 of 40 patients (38%) receiving 1 mg/kg/day for 6 months (P=0.004 for the comparison with placebo), and 27 of 43 patients (63%) receiving 3 mg/kg/day for 6 months (P<0.001 for the comparison with placebo). Overall, 61 of 101 patients (60%) assigned to the selected propranolol regimen and 2 of 55 patients (4%) assigned to placebo had successful treatment at week 24 (P<0.001). Improvement between baseline and week 5 (according to centralized assessment) occurred in 88% of patients assigned to the selected regimen and 5% of patients assigned to placebo (P<0.001). Secondary: Not reported

*Agent not available in the United States.
Drug regimen abbreviations: BID=twice daily, CR=controlled-release, ER=extended-release, QD=once daily, SR=sustained-release, TID=three times daily, XL=extended-release
Study design abbreviations: AC=active comparator, BE=blinded endpoint, DB=double blind, DD=double dummy, MA=meta analysis, MC=multicenter, OL=open label, PC=placebo controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, SB=single blind, XO=cross over
Miscellaneous abbreviations: ACE inhibitor=angiotensin converting enzyme inhibitor, AF=atrial fibrillation, AIx=augmentation index, aPWV=aortic pulse wave velocity, ARB=angiotensin II receptor blocker, CABG=coronary artery bypass graft, CAD=coronary artery disease, CHD=coronary heart disease, CHF=congestive heart failure, CI=confidence interval, COPD=chronic obstructive pulmonary disease, DBP=diastolic blood pressure, ECG=electrocardiogram, ESRD=end stage renal disease, FEV_1=forced expiratory volume in one second, GFR=glomerular filtration rate, HDL-C=high-density lipoprotein cholesterol, HR=hazard ratio, HTN=hypertension, LDL-C=low-density lipoprotein cholesterol, LVEF=left ventricular ejection fraction, MAP=mean arterial pressure, MI=myocardial infarction, NYHA=New York Heart Association, OR=odds ratio, PAD=peripheral arterial disease, pro-BNP= pro-B-type natriuretic peptide, PVD=peripheral vascular disease, QOL=quality of life, RMSSD=root mean square of successive RR intervals, RR=relative risk, SBP=systolic blood pressure, SDNN=standard deviation of the normal RR intervals, TC=total cholesterol, TG=triglyceride, TIA=transient ischemic attack, WHO=World Health Organization

Additional Evidence

Dose Simplification
Nissinen et al. evaluated newly diagnosed hypertensive patients who received atenolol 100 mg and chlorthalidone 25 mg given as single entity products or as a fixed-dose combination. Each of the active drug combinations significantly lowered standing, supine and postexercise blood pressure. There was no significant difference among the treatment regimens.[96]

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 18. Relative Cost of the Beta-Adrenergic Blocking Agents

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Acebutolol	capsule	N/A	N/A	$$$
Atenolol	tablet	Tenormin®*	$$$$$	$$
Betaxolol	tablet	N/A	N/A	$$
Bisoprolol	tablet	N/A	N/A	$
Carvedilol	extended-release capsule, tablet	Coreg®*, Coreg CR®*	$$$$$	$
Labetalol	injection, tablet	N/A	N/A	$
Metoprolol	extended-release capsule, extended-release tablet, injection, tablet	Kapspargo Sprinkle®, Lopressor®*, Toprol-XL®*	$$$	$
Nadolol	tablet	N/A	N/A	$
Nebivolol	tablet	Bystolic®*	$$$$	$
Penbutolol	tablet	Levatol®	N/A†	N/A
Pindolol	tablet	N/A	N/A	$$

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Propranolol	extended-release capsule, injection, solution, tablet	Hemangeol®, Inderal LA®*, Inderal XL®, InnoPran XL®	$$$$$	$
Sotalol	tablet, solution	Betapace®*, Betapace AF®*, Sotylize®	$$$$$	$
Timolol	tablet	N/A	N/A	$$$$
Combination Products				
Atenolol and chlorthalidone	tablet	Tenoretic®*	$$$$	$
Bisoprolol and HCTZ	tablet	Ziac®*	$$$$$	$
Metoprolol and HCTZ	tablet	N/A	N/A	$$$
Nadolol and bendroflumethiazide	tablet	N/A	N/A	$$$

*Generic is available in at least one dosage form or strength.
†Product was discontinued by manufacturer, but remains active in pharmacy system. Pricing information not available.
HCTZ=hydrochlorothiazide, N/A=not available

X. Conclusions

All of the beta-adrenergic blocking agents (β-blockers) are approved for the treatment of hypertension, with the exception of sotalol.[1-3] Some of the products are also approved for the treatment of angina, arrhythmias, essential tremor, heart failure, hypertension, hypertrophic aortic stenosis, infantile hemangiomas, migraine prophylaxis, myocardial infarction, and pheochromocytoma.[1-3] These agents differ with regards to their adrenergic-receptor blockade, membrane stabilizing and intrinsic sympathomimetic activities, as well as lipophilicity.[1,2,6] All of the agents are available in a generic formulation, with the exception of penbutolol.

Several national and international guidelines address the use of β-blockers.[7-38] Due to improvements in cardiovascular morbidity and mortality, treatment guidelines recommend the use of a β-blocker in patients with the following conditions: acute coronary syndromes, angina, arrhythmias, coronary artery disease, heart failure, left ventricular dysfunction, post-myocardial infarction, and infantile hemangiomas.[7-38] There are several published guidelines on the treatment of hypertension. Thiazide-type diuretics are frequently recommended as initial therapy in patients with uncomplicated hypertension.[21-29] According to the National Heart, Lung, and Blood Institute's Eighth Report of The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8), thiazide-type diuretics should be utilized first-line for most patients with hypertension, either alone or in combination with another hypertensive from a different medication class (e.g., ACE inhibitors, ARBs, β-blockers, calcium channel blockers).[21] Several guidelines consistently recommend that the selection of an antihypertensive agent be based on compelling indications for use.[21-29] Most patients will require more than one antihypertensive medication to achieve blood pressure goals.[21-28] β-blockers are recommended as one of several initial options for the prevention of migraine headaches (metoprolol, propranolol, and timolol), as well as for the treatment of essential tremor (propranolol).[30-34,36,37] The Clinical Practice Guideline for the Management of Infantile Hemangiomas was published in January 2019 and recommends the use of oral propranolol as the first-line agent for the treatment.[38] The oral solution formulation of propranolol, under the brand name Hemangeol®, is the first agent to gain FDA-approval for this indication.[1-3]

Numerous clinical trials have shown that the β-blockers can effectively lower blood pressure when administered alone or in combination with other antihypertensive agents. Comparative studies have demonstrated similar efficacy among the β-blockers.[84-130] Most patients will require more than one antihypertensive agent to achieve blood pressure goals.[21-28] The use of a fixed-dose combination product may simplify the treatment regimen and improve adherence.[24,25] However, there are no prospective, randomized trials that have demonstrated better clinical outcomes with a fixed-dose combination product compared to the coadministration of the individual components as separate formulations.[87]

In patients with chronic stable angina, β-blockers improve exercise tolerance and reduce the frequency of attacks. Head-to-head trials have demonstrated similar efficacy among several of the β-blockers.[39-47] In patients with heart

failure, β-blockers (bisoprolol, carvedilol, and metoprolol succinate) have been shown to reduce mortality, sudden death, cardiovascular deaths, and death due to heart failure. Clinical trials supporting the use of carvedilol in patients with mild-to-severe heart failure were conducted with the immediate-release formulation.[58-65,68,69,73-75,78-80] Data to support the use of the extended-release capsules for the treatment of heart failure is based on pharmacokinetic and pharmacodynamic parameters that demonstrated bioequivalence with the immediate-release formulation.[3]

In general, adverse events are similar among the β-blockers. Common adverse effects include fatigue, cold hands, dizziness, and weakness.[1-3] β-blockers that are more selective for the β_1-receptors (atenolol and metoprolol) may be safer to use in those with reactive airway disease as they are less likely to cause bronchospasm.[4,6]

There is insufficient evidence to support that one brand beta-adrenergic blocking agent is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand beta-adrenergic blocking agents within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand beta-adrenergic blocking agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Dihydropyridines
AHFS Class 242808
May 8, 2024

I. Overview

The movement of calcium ions is essential for the function of all types of muscle, including cardiac and vascular smooth muscle. When this flow is reduced, the result is a weakening of muscle contraction and relaxation of muscle tissue.[1-3] Relaxation of coronary vascular smooth muscle increases the flow of oxygenated blood into the myocardium, while relaxation of arteriolar smooth muscle decreases peripheral vascular resistance.[3-4] Both coronary and systemic vasodilation serve to reduce cardiac workload. The calcium-channel blocking agents include dihydropyridines and nondihydropyridines. Although they have different binding sites on the L-type calcium channel, both block the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. The nondihydropyridines also block the T-type calcium channel in the atrioventricular node.[1-4]

The dihydropyridines are approved for the treatment of angina and hypertension. Amlodipine is also indicated to reduce the risk of hospitalization due to angina and to reduce the risk of a coronary revascularization procedure in patients with recently documented coronary artery disease.[1,2,5-17] They are potent vasodilators and have little effect on cardiac muscle contractility or conduction. The dihydropyridines are available in a variety of single entity formulations. Amlodipine is also available in combination with benazepril, olmesartan, valsartan, or valsartan-hydrochlorothiazide. Angiotensin converting enzyme (ACE) inhibitors block the conversion of angiotensin I to angiotensin II, and also inhibit the breakdown of bradykinin, a potent vasodilator. Angiotensin II receptor antagonists block the angiotensin II receptor subtype AT_1, preventing the negative effects of angiotensin II, regardless of its origin. Hydrochlorothiazide inhibits the reabsorption of sodium and chloride in the cortical thick ascending limb of the loop of Henle and the early distal tubules. This action leads to an increase in the urinary excretion of sodium and chloride.[1,2]

The dihydropyridines that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All of the products with the exception of clevidipine are available in a generic formulation. This class was last reviewed in May 2022.

Table 1. Dihydropyridines Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Amlodipine	solution, suspension, tablet	Katerzia®, Norliqva®, Norvasc®*	amlodipine
Clevidipine	injection^	Cleviprex®	none
Felodipine	extended-release tablet	N/A	felodipine
Isradipine	capsule	N/A	isradipine
Levamlodipine	tablet	N/A	none
Nicardipine	capsule*, injection*	Cardene-NACL®^*	nicardipine
Nifedipine	capsule, extended-release tablet	Adalat CC®*, Procardia XL®*	nifedipine
Nimodipine	capsule*, solution	Nymalize®	nimodipine
Nisoldipine	extended-release tablet*	Sular ER®*	nisoldipine
Combination Products			
Amlodipine and benazepril	capsule	Lotrel®*	amlodipine and benazepril
Amlodipine and olmesartan	tablet	Azor®*	amlodipine and olmesartan
Amlodipine and valsartan	tablet	Exforge®*	amlodipine and valsartan
Amlodipine, valsartan, and hydrochlorothiazide	tablet	Exforge HCT®*	amlodipine, valsartan, and hydrochlorothiazide

*Generic is available in at least one dosage form or strength.
^Product is primarily administered in an institution.
PDL=Preferred Drug List

N/A=Not available

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the dihydropyridines are summarized in Table 2.

Table 2. Treatment Guidelines Using the Dihydropyridines

Clinical Guideline	Recommendations
American Heart Association/American College of Cardiology/American College of Clinical Pharmacy/American Society for Preventive Cardiology/National Lipid Association/ Preventive Cardiovascular Nurses Association **Guideline for the Management of Patients With Chronic Coronary Disease (2023)**[18]	• In patients with chronic coronary disease (CCD), high-intensity statin therapy is recommended with the aim of achieving a ≥50% reduction in LDL-C levels to reduce the risk of major adverse cardiovascular events (MACE). • In patients in whom high-intensity statin therapy is contraindicated or not tolerated, moderate-intensity statin therapy is recommended with the aim of achieving a 30% to 49% reduction in LDL-C levels to reduce the risk of MACE. • In patients with CCD who are judged to be at very high risk and on maximally tolerated statin therapy with an LDL-C level ≥70 mg/dL, ezetimibe can be beneficial to further reduce the risk of MACE. • In patients with CCD who are judged to be at very high risk and who have an LDL-C level ≥70 mg/dL, or a non–high-density lipoprotein cholesterol (HDL-C) level ≥100 mg/dL, on maximally tolerated statin and ezetimibe, a PCSK9 monoclonal antibody can be beneficial to further reduce the risk of MACE. • In patients with CCD on maximally tolerated statin therapy with an LDL-C level <100 mg/dL and a persistent fasting triglyceride level of 150 to 499 mg/dL after addressing secondary causes, icosapent ethyl may be considered to further reduce the risk of MACE and cardiovascular death. • In patients with CCD who are not at very high risk and on maximally tolerated statin therapy with an LDL-C level ≥70 mg/dL, it may be reasonable to add ezetimibe to further reduce the risk of MACE. • In patients with CCD on maximally tolerated statin therapy who have an LDL-C level ≥70 mg/dL, and in whom ezetimibe and PCSK9 monoclonal antibody are deemed insufficient or not tolerated, it may be reasonable to add bempedoic acid or inclisiran (in place of PCSK9 monoclonal antibody) to further reduce LDL-C levels. • In patients with CCD receiving statin therapy, adding niacin, fenofibrate, or dietary supplements containing omega-3 fatty acids are not beneficial in reducing cardiovascular risk. • In adults with CCD, nonpharmacologic strategies are recommended as first-line therapy to lower BP in those with elevated BP (120-129/<80 mmHg). • In adults with CCD who have hypertension, a BP target of <130/<80 mmHg is recommended to reduce CVD events and all-cause death. • In adults with CCD and hypertension (systolic BP ≥130 and/or diastolic BP ≥80 mm Hg), in addition to nonpharmacological strategies, GDMT angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), or beta blockers are recommended as first-line therapy for compelling indications (e.g., recent MI or angina), with additional antihypertensive medications (e.g., dihydropyridine calcium channel blockers [CCB], long-acting thiazide diuretics, and/or mineralocorticoid receptor antagonists) added as needed to optimize BP control. • In patients with CCD and no indication for oral anticoagulant therapy, low-dose aspirin 81 mg (75 to 100 mg) is recommended to reduce atherosclerotic events. • In patients with CCD treated with PCI, dual antiplatelet therapy (DAPT) consisting of aspirin and clopidogrel for 6 months post PCI followed by single antiplatelet therapy (SAPT) is indicated to reduce MACE and bleeding events.* • In select patients with CCD treated with PCI and a drug-eluting stent (DES) who have completed a 1- to 3-month course of DAPT, P2Y12 inhibitor monotherapy

Clinical Guideline	Recommendations
	for at least 12 months is reasonable to reduce bleeding risk. • In patients with CCD who have had a previous MI and are at low bleeding risk, extended DAPT beyond 12 months for a period of up to 3 years may be reasonable to reduce MACE. • In patients with CCD and a previous history of MI without a history of stroke, transient ischemic attack (TIA), or ICH, vorapaxar may be added to aspirin therapy to reduce MACE. • In patients with CCD, the use of DAPT after CABG may be useful to reduce the incidence of saphenous vein graft occlusion. • In patients with CCD without recent ACS or a PCI-related indication for DAPT, the addition of clopidogrel to aspirin therapy is not useful to reduce MACE. • In patients with CCD and previous stroke, TIA, or ICH, vorapaxar should not be added to DAPT because of increased risk of major bleeding and ICH. • In patients with CCD and previous stroke, TIA, or ICH, prasugrel should not be used because of risk of significant or fatal bleeding. • In patients with CCD, chronic nonsteroidal anti-inflammatory drugs should not be used because of increased cardiovascular and bleeding complications. • In patients with CCD who have undergone elective PCI and who require oral anticoagulant therapy, DAPT for one to four weeks followed by clopidogrel alone for six months should be administered in addition to DOAC. • In patients with CCD who have undergone PCI and who require oral anticoagulant therapy, continuing aspirin in addition to clopidogrel for up to 1 month is reasonable if the patient has a high thrombotic risk and low bleeding risk. • In patients with CCD who require oral anticoagulation and have a low atherothrombotic risk, discontinuation of aspirin therapy with continuation of DOAC alone may be considered one year after PCI to reduce bleeding risk. • In patients with CCD who require oral anticoagulation, DOAC monotherapy may be considered if there is no acute indication for concomitant antiplatelet therapy. • In patients with CCD without an indication for therapeutic DOAC or DAPT and who are at high risk of recurrent ischemic events but low-to-moderate bleeding risk, the addition of low-dose rivaroxaban 2.5 mg twice daily to aspirin 81 mg daily is reasonable for long-term reduction of risk for MACE. • In patients with CCD on DAPT, the use of a PPI can be effective in reducing gastrointestinal bleeding risk. • In patients with CCD and LVEF ≤40% with or without previous MI, the use of beta-blocker therapy is recommended to reduce the risk of future MACE, including cardiovascular death. • In patients with CCD and LVEF<50%, the use of sustained release metoprolol succinate, carvedilol, or bisoprolol with titration to target doses is recommended in preference to other beta blockers. • In patients with CCD who were initiated on beta-blocker therapy for previous MI without a history of or current LVEF ≤50%, angina, arrhythmias, or uncontrolled hypertension, it may be reasonable to reassess the indication for long-term (>1 year) use of beta-blocker therapy for reducing MACE. • In patients with CCD without previous MI or LVEF ≤50%, the use of beta-blocker therapy is not beneficial in reducing MACE, in the absence of another primary indication for beta-blocker therapy. • In patients with CCD who also have hypertension, diabetes, LVEF ≤40%, or CKD, the use of ACE inhibitors, or ARBs if ACE inhibitor–intolerant, is recommended to reduce cardiovascular events. • In patients with CCD without hypertension, diabetes, or CKD and LVEF >40%, the use of ACE inhibitors or ARBs may be considered to reduce cardiovascular events. • In patients with CCD, the addition of colchicine for secondary prevention may be

Clinical Guideline	Recommendations
	considered to reduce recurrent ASCVD events. • In patients with CCD, an annual influenza vaccination is recommended to reduce cardiovascular morbidity, cardiovascular death, and all-cause death. • In patients with CCD, coronavirus disease 2019 (COVID-19) vaccination is recommended per public health guidelines to reduce COVID-19 complications. • In patients with CCD, a pneumococcal vaccine is reasonable to reduce cardiovascular morbidity and mortality and all-cause death. • In patients with CCD and angina, antianginal therapy with either a beta blocker, CCB, or long-acting nitrate is recommended for relief of angina or equivalent symptoms. • In patients with CCD and angina who remain symptomatic after initial treatment, addition of a second antianginal agent from a different therapeutic class (beta blockers, CCB, long-acting nitrates) is recommended for relief of angina or equivalent symptoms. • In patients with CCD, ranolazine is recommended in patients who remain symptomatic despite treatment with beta blockers, CCB, or long-acting nitrate therapies. • In patients with CCD, sublingual nitroglycerin or nitroglycerin spray is recommended for immediate short-term relief of angina or equivalent symptoms. • In patients with CCD and normal LV function, the addition of ivabradine to standard anti-anginal therapy is potentially harmful. • In patients with CCD and lifestyle-limiting angina despite GDMT and with significant coronary artery stenoses amenable to revascularization, revascularization is recommended to improve symptoms. • In patients with CCD who have experienced SCAD, beta-blocker therapy may be reasonable to reduce the incidence of recurrent SCAD. • Women with CCD who are contemplating pregnancy or who are pregnant should not use ACE inhibitors, ARBs, direct renin inhibitors, angiotensin receptor-neprilysin inhibitors, or aldosterone antagonists during pregnancy to prevent harm to the fetus. • Women with CCD should not receive systemic postmenopausal hormone therapy because of a lack of benefit on MACE and mortality, and an increased risk of venous thromboembolism.

European Society of Cardiology: **Guidelines for the Diagnosis and Management of Chronic Coronary Syndromes (2019)**[19]	<u>Pharmacological management of stable coronary artery disease (CAD) patients</u>
	• The two aims of the pharmacological management of stable CAD patients are to obtain relief of symptoms and to prevent CV events.
	• Optimal medical treatment indicates at least one drug for angina/ischaemia relief plus drugs for event prevention.
	• It is recommended to educate patients about the disease, risk factors and treatment strategy.
	• It is indicated to review the patient's response soon after starting therapy.
	• Concomitant use of a proton pump inhibitor is recommended in patients receiving aspirin monotherapy, DAPT, or DOAC monotherapy who are at high risk of gastrointestinal bleeding.
	• Lipid-lowering drugs: if goals are not met on maximum tolerated dose of a statin, consideration of combination therapy with ezetimibe or a PCSK9 inhibitor is recommended
	• ACE inhibitors should be considered in patients at a very high risk of cardiovascular adverse events
	• Angina/ischemia relief:
	  ○ Short-acting nitrates are recommended.
	  ○ First-line treatment is indicated with ß-blockers and/or calcium channel blockers to control heart rate and symptoms.
	  ○ Long-acting nitrates should be considered as a second-line treatment

Clinical Guideline	Recommendations
	option when initial therapy with a ß -blocker and/or a non-DHP-calcium channel blocker is contraindicated, poorly tolerated, or inadequate in controlling angina symptoms o Nicorandil, ranolazine, ivabradine, or trimetazidine should be considered as a second-line treatment to reduce angina frequency and improve exercise tolerance in subjects who cannot tolerate, have contraindications to, or whose symptoms are not adequately controlled by beta-blockers, CCBs, and long-acting nitrates. o According to comorbidities/tolerance, it is indicated to use second-line therapies as first-line treatment in selected patients. o In asymptomatic patients with large areas of ischaemia (>10%) ß-blockers should be considered. o In patients with vasospastic angina, calcium channel blockers and nitrates should be considered and beta-blockers avoided. • Event prevention: o Low-dose aspirin daily is recommended in all stable CAD patients. o Clopidogrel is indicated as an alternative in case of aspirin intolerance. o Statins are recommended in all stable CAD patients. o It is recommended to use ACE inhibitors (or ARBs) if presence of other conditions (e.g., heart failure, hypertension or diabetes). <u>Treatment in patients with microvascular angina</u> • It is recommended that all patients receive secondary prevention medications including aspirin and statins. • ß-blockers are recommended as a first-line treatment. • Calcium antagonists are recommended if ß-blockers do not achieve sufficient symptomatic benefit or are not tolerated. • ACE inhibitors or nicorandil may be considered in patients with refractory symptoms. • Xanthine derivatives or nonpharmacological treatments such as neurostimulatory techniques may be considered in patients with symptoms refractory to the above listed drugs. <u>Stenting and peri-procedural antiplatelet strategies in stable CAD patients</u> • Drug-eluting stent (DES) is recommended in stable CAD patients undergoing stenting if there is no contraindication to prolonged dual antiplatelet therapy (DAPT). • Aspirin is recommended for elective stenting. • Clopidogrel is recommended for elective stenting. • Prasugrel or ticagrelor should be considered in patients with stent thrombosis on clopidogrel without treatment interruption. • GP IIb/IIIa antagonists should be considered for bailout situation only. • Platelet function testing or genetic testing may be considered in specific or high risk situations (e.g., prior history of stent thrombosis; compliance issue; suspicion of resistance; high bleeding risk) if results may change the treatment strategy. • Prasugrel or ticagrelor may be considered in specific high-risk situations of elective stenting (e.g., left main stenting, high risk of stent thrombosis, diabetes). • Pretreatment with clopidogrel (when coronary anatomy is not known) is not recommended. • Routine platelet function testing (clopidogrel and aspirin) to adjust antiplatelet therapy before or after elective stenting is not recommended. • Prasugrel or ticagrelor is not recommended in low-risk elective stenting. • After uncomplicated PCI, early cessation (≤1 week) of aspirin, and continuation of dual therapy with oral anticoagulation therapy and clopidogrel should be

Clinical Guideline	Recommendations
	considered if the risk of stent thrombosis is low • Triple therapy with aspirin, clopidogrel, and a DOAC for ≥1 month should be considered when the risk of stent thrombosis outweighs the bleeding risk, with a total of no more than six months <u>Follow-up of revascularized stable coronary artery disease patients</u> • It is recommended that all revascularized patients receive a secondary prevention and be scheduled for follow-up visit. • It is recommended to instruct patients before discharge about return to work and reuptake of full activities. Patients have to be advised to seek immediate medical contact if symptoms (re-) occur. • Single antiplatelet therapy, usually aspirin, is recommended indefinitely. • DAPT is indicated after bare metal stent (BMS) for at least one month. • DAPT is indicated for six to 12 months after second generation DES. • DAPT may be used for more than one year in patients at high ischemic risk (e.g., stent thrombosis, recurrent acute coronary syndrome on DAPT, post MI/diffuse CAD) and low bleeding risk. • DAPT for one to three months may be used after DES implantation in patients at high bleeding risk or with undeferrable surgery or concomitant anticoagulant treatment. <u>Antithrombotic therapy in patients with chronic coronary syndrome:</u> • Addition of a second antithrombotic drug to aspirin for long-term secondary prevention should be considered in patients with at least a moderately increased risk of ischemic events and without high bleeding risk • When oral anticoagulation is initiated in patients with AF, a DOAC is recommended in preference to VKA therapy.
American College of Cardiology Foundation/American Heart Association: **2014 American Heart Association/ American College of Cardiology Foundation Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes (2014)[20]**	<u>Early hospital care- standard medical therapies</u> • Supplemental oxygen should be administered to patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) with arterial oxygen saturation <90%, respiratory distress, or other high risk features of hypoxemia. • Anti-ischemic and analgesic medications o Nitrates ▪ Patients with NSTE-ACS with continuing ischemic pain should receive sublingual nitroglycerin (0.3 to 0.4 mg) every 5 minutes for up to three doses, after which an assessment should be made about the need for intravenous nitroglycerin. ▪ Intravenous nitroglycerin is indicated for patients with NSTE-ACS for the treatment of persistent ischemia, heart failure, or hypertension. ▪ Nitrates should not be administered to patients who recently received a phosphodiesterase inhibitor, especially within 24 hours of sildenafil or vardenafil, or within 48 hours of tadalafil. o Analgesic therapy ▪ In the absence of contraindications, it may be reasonable to administer morphine sulphate intravenously to patients with NSTE-ACE if there is continued ischemic chest pain despite treatment with maximally tolerated anti-ischemic medications. ▪ Nonsteroidal anti-inflammatory drugs (NSAIDs) (except aspirin) should not be initiated and should be discontinued during hospitalization due to the increased risk of major adverse cardiac event associated with their use o Beta-adrenergic blockers ▪ Oral β-blocker therapy should be initiated within the first 24 hours in patients who do not have any of the following: 1) signs of HF, 2) evidence of low-output state, 3) increased risk for cardiogenic shock, or

Clinical Guideline	Recommendations
	4) other contraindications to β-blockade (e.g., PR interval >0.24 second, second- or third-degree heart block without a cardiac pacemaker, active asthma, or reactive airway disease) ▪ In patients with concomitant NSTE-ACS, stabilized heart failure, and reduced systolic function, it is recommended to continue β-blocker therapy with one of the three drugs proven to reduce mortality in patients with heart failure: sustained-release metoprolol succinate, carvedilol, or bisoprolol. ▪ Patients with documented contraindications to β-blockers in the first 24 hours should be re-evaluated to determine subsequent eligibility. o Calcium channel blockers (CCBs) ▪ In patients with NSTE-ACS, continuing or frequently recurring ischemia, and a contraindication to β-blockers, a nondihydropyridine CCB (e.g., verapamil or diltiazem) should be given as initial therapy in the absence of clinically significant LV dysfunction, increased risk for cardiogenic shock, PR interval >0.24 seconds, or second or third degree atrioventricular block without a cardiac pacemaker. ▪ Oral nondihydropyridine calcium antagonists are recommended in patients with NSTE-ACS who have recurrent ischemia in the absence of contraindications, after appropriate use of β-blockers and nitrates. ▪ CCBs are recommended for ischemic symptoms when β-blockers are not successful, are contraindicated, or cause unacceptable side effects. ▪ Long-acting CCBs and nitrates are recommended in patients with coronary artery spasm. ▪ Immediate-release nifedipine should not be administered to patients with NSTE-ACS in the absence of β-blocker therapy. o Other anti-ischemic interventions ▪ Ranolazine is currently indicated for treatment of chronic angina; however, it may also improve outcomes in NSTE-ACS patients due to a reduction in recurrent ischemia. o Cholesterol management ▪ High-intensity statin therapy should be initiated or continued in all patients with NSTE-ACS and no contraindications to its use. Treatment with statins reduces the rate of recurrent MI, coronary heart disease mortality, need for myocardial revascularization, and stroke. ▪ It is reasonable to obtain a fasting lipid profile in patients with NSTE-ACS, preferably within 24 hours of presentation. • Inhibitors of renin-angiotensin-aldosterone system o ACE inhibitors should be started and continued indefinitely in all patients with LVEF <0.40 and in those with hypertension, diabetes mellitus, or stable CKD, unless contraindicated. o ARBs are recommended in patients with heart failure or myocardial infarction with LVEF <0.40 who are ACE inhibitor intolerant. o Aldosterone-blockade is recommended in patients post-MI without significant renal dysfunction (creatinine >2.5 mg/dL in men or >2.0 mg/dL in women) or hyperkalemia (K >5.0 mEq/L) who are receiving therapeutic doses of ACE inhibitor and β-blocker and have a LVEF <0.40, diabetes mellitus, or heart failure. • Initial antiplatelet/anticoagulant therapy in patients with definite or likely NSTE-ACS treated with an initial invasive or ischemia-guided strategy o Non-enteric coated, chewable aspirin (162 to 325 mg) should be given to all patients with NSTE-ACS without contraindications as soon as possible after presentation, and a maintenance dose of aspirin (81 to 162 mg/day) should be continued indefinitely. o In patients who are unable to take aspirin because of hypersensitivity or major

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	gastrointestinal intolerance, a loading dose of clopidogrel followed by a daily maintenance dose should be administered. o A $P2Y_{12}$ receptor inhibitor (clopidogrel or ticagrelor) in addition to aspirin should be administered for up to 12 months to all patients with NSTE-ACS without contraindications who are treated with an early invasive or ischemia-guided strategy. Options include: ▪ Clopidogrel: 300 or 600 mg loading dose, then 75 mg daily. ▪ Ticagrelor: 180 mg loading dose, then 90 mg twice daily. ▪ It is reasonable to use ticagrelor in preference to clopidogrel for $P2Y_{12}$ treatment in patients with NSTE-ACS who undergo an early invasive or ischemia-guided strategy. ▪ In patients with NSTE-ACS treated with an early invasive strategy and dual antiplatelet therapy (DAPT) with intermediate/high-risk features (e.g., positive troponin), a GP IIb/IIIa inhibitor may be considered as part of initial antiplatelet therapy. Preferred options are eptifibatide or tirofiban. <u>Percutaneous coronary intervention (PCI)- Antiplatelet and anticoagulant therapy</u> • Antiplatelet agents o Patients already taking daily aspirin before PCI should take 81 to 325 mg non-enteric coated aspirin before PCI o Patients not on aspirin therapy should be given non-enteric coated aspirin 325 mg as soon as possible before PCI. o After PCI, aspirin should be continued indefinitely. o A loading dose of a $P2Y_{12}$ inhibitor should be given before the procedure in patients undergoing PCI with stenting. Options include clopidogrel 600 mg, prasugrel 60 mg, or ticagrelor 180 mg. o In patients with NSTE-ACS and high-risk features (e.g., elevated troponin) not adequately pretreated with clopidogrel or ticagrelor, it is useful to administer a GP IIb/IIIa inhibitor (abciximab, double-bolus eptifibatide, or high-dose bolus tirofiban) at the time of PCI. o In patients receiving a stent (bare metal or drug eluting) during PCI, $P2Y_{12}$ inhibitor therapy should be given for at least 12 months. Options include clopidogrel 75 mg daily, prasugrel 10 mg daily, or ticagrelor 90 mg twice daily. • Anticoagulant therapy o An anticoagulant should be administered to patients with NSTE-ACS undergoing PCI to reduce the risk of intracoronary and catheter thrombus formation. o Intravenous unfractionated heparin (UFH) is useful in patients with NSTE-ACS undergoing PCI. o Bivalirudin is useful as an anticoagulant with or without prior treatment with UFH. o An additional dose of 0.3 mg/kg intravenous enoxaparin should be administered at the time of PCI to patients with NSTE-ACS who have received fewer than two therapeutic subcutaneous doses or received the last subcutaneous enoxaparin dose eight to 12 hours before PCI. o If PCI is performed while the patient is on fondaparinux, an additional 85 IU/kg of UFH should be given intravenously immediately before PCI because of the risk of catheter thrombosis (60 IU/kg IV if a GP IIb/IIIa inhibitor used with UFH dosing based on the target-activated clotting time). o Anticoagulant therapy should be discontinued after PCI unless there is a compelling reason to continue. • Timing of CABG in relation to use of antiplatelet agents o Non-enteric coated aspirin (81 to 325 mg daily) should be administered

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	preoperatively to patients undergoing CABG. o In patients referred for elective CABG, clopidogrel and ticagrelor should be discontinued for at least five days before surgery and prasugrel for at least seven days before surgery. o In patients referred for urgent CABG, clopidogrel and ticagrelor should be discontinued for at least 24 hours to reduce major bleeding. o In patients referred for CABG, short-acting intravenous GP IIb/IIIa inhibitors (eptifibatide or tirofiban) should be discontinued for at least 2 to 4 hours before surgery and abciximab for at least 12 hours before to limit blood loss and transfusion. <u>Late hospital care, hospital discharge, and posthospital discharge care</u> • Medications at discharge o Medications required in the hospital to control ischemia should be continued after hospital discharge in patients with NSTE-ACS who do not undergo coronary revascularization, patients with incomplete or unsuccessful revascularization, and patients with recurrent symptoms after revascularization. Titration of the doses may be required. o All patients who are post–NSTE-ACS should be given sublingual or spray nitroglycerin with verbal and written instructions for its use. o Before hospital discharge, patients with NSTE-ACS should be informed about symptoms of worsening myocardial ischemia and MI and should be given verbal and written instructions about how and when to seek emergency care for such symptoms. o Before hospital discharge, patients who are post–NSTE-ACS and/or designated responsible caregivers should be provided with easily understood and culturally sensitive verbal and written instructions about medication type, purpose, dose, frequency, side effects, and duration of use. o For patients who are post–NSTE-ACS and have initial angina lasting more than one minute, nitroglycerin (one dose sublingual or spray) is recommended if angina does not subside within three to five minutes; call 9-1-1 immediately to access emergency medical services. o If the pattern or severity of angina changes, suggesting worsening myocardial ischemia (e.g., pain is more frequent or severe or is precipitated by less effort or occurs at rest), patients should contact their clinician without delay to assess the need for additional treatment or testing. o Before discharge, patients should be educated about modification of cardiovascular risk factors. • Late hospital and post-hospital oral antiplatelet therapy o Aspirin should be continued indefinitely. The dose should be 81 mg daily in patients treated with ticagrelor and 81 to 325 mg daily in all other patients. o In addition to aspirin, a $P2Y_{12}$ inhibitor (either clopidogrel or ticagrelor) should be continued for up to 12 months in all patients with NSTE-ACS without contraindications who are treated with an ischemia-guided strategy. o In patients receiving a stent (bare-metal stent or DES) during PCI for NSTE-ACS, P2Y12 inhibitor therapy should be given for at least 12 months. • Combined oral anticoagulant therapy and antiplatelet therapy in patients with NSTE-ACS o The duration of triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a $P2Y_{12}$ receptor inhibitor in patients with NSTE-ACS should be minimized to the extent possible to limit the risk of bleeding. o Proton pump inhibitors should be prescribed in patients with NSTE-ACS with a history of gastrointestinal bleeding who require triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a $P2Y_{12}$ receptor inhibitor.
American College of	<u>Routine medical therapies: calcium channel blockers</u>

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Cardiology/American Heart Association: **Guideline for the Management of ST-Elevation Myocardial Infarction (2013)**[21]	• Evidence demonstrates that beneficial effect on infarct size or the rate of reinfarction when calcium channel blocker therapy was initiated during either the acute or convalescent phase of ST-segment elevation myocardial infarction (STEMI). However, calcium channel blockers may be useful to relieve ischemia, lower blood pressure, or control the ventricular response rate to atrial fibrillation in patients who are intolerant to β-blockers. • Use of immediate-release nifedipine is contraindicated in patients with STEMI due to hypotension and reflex sympathetic activation with tachycardia. <u>Routine medical therapies: β-blockers</u> • Oral β-blockers should be initiated within the first 24 hours in patients with an ST-segment elevation myocardial infarction (STEMI) who do not have any of the following: 1) signs of heart failure, 2) evidence of a low-output state, 3) increased risk of cardiogenic shock, 4) other contraindications to use of oral β-blockers (e.g., PR interval >24 seconds, second or third degree heart block, active asthma, reactive airway disease). • β-blockers should be continued during and after hospitalization for all patients with STEMI and with no contraindications to their use. • Patients with initial contraindications to the use of β-blockers in the first 24 hours after STEMI should be re-evaluated to determine their subsequent eligibility. • It is reasonable to administer intravenous β-blockers at the time of presentation to patients with STEMI and no contraindications to their use who are hypertensive or have ongoing ischemia. <u>Routine medical therapies: Renin-Angiotensin-Aldosterone System Inhibitors</u> • An angiotensin-converting enzyme (ACE) inhibitor should be administered within the first 24 hours to all patients with STEMI with anterior location, HF, or ejection fraction (EF) ≤40%, unless contraindicated. • An angiotensin receptor blocker (ARB) should be given to patients with STEMI who have indications for but are intolerant of ACE inhibitors. • An aldosterone antagonist should be given to patients with STEMI and no contraindications who are already receiving an ACE inhibitor and β-blocker and who have an EF ≤40% and either symptomatic heart failure or diabetes. <u>Routine medical therapies: Lipid management</u> • High-intensity statin therapy should be initiated or continued in all patients with STEMI and no contraindications to its use. • It is reasonable to obtain a fasting lipid profile in patients with STEMI, preferably within 24 hours of presentation.
European Society of Cardiology: **Management of Acute Myocardial Infarction in Patients Presenting with ST-segment Elevation (2017)**[22]	<u>Routine therapies in the acute, subacute and long term phase of ST-elevation myocardial infarction (STEMI)</u> • Antiplatelet therapy with low dose aspirin (75 to 100 mg) is indicated indefinitely after STEMI. • Dual antiplatelet therapy with a combination of aspirin and prasugrel or aspirin and ticagrelor is recommended for 12 months after percutaneous coronary intervention (PCI), unless there are contraindications such as excessive risk of bleeding. • A proton pump inhibitor (PPI) in combination with dual antiplatelet therapy is recommended in patients at high risk of gastrointestinal bleeding. • In patients with an indication for oral anticoagulation, oral anticoagulants are indicated in addition to antiplatelet therapy. • In patients who are at high risk of severe bleeding complications, discontinuation of $P2Y_{12}$ inhibitor therapy after six months should be considered. • In STEMI patients with stent implantation and an indication for oral

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	anticoagulation, triple therapy (oral anticoagulant, aspirin, and clopidogrel) should be considered for one to six months (according a balance between the estimated risk of recurrent coronary events and bleeding). • In patients with left ventricular thrombus, anticoagulation should be instituted for a minimum of six months, guided by repeated imaging. • In selected patients who receive aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily) may be considered if the patient is at low bleeding risk. • Dual antiplatelet therapy should be used up to one year in patients with STEMI who did not receive a stent unless there are contraindications such as excessive risk of bleeding. • In high ischemic-risk patients (age ≥50 years, and at least one of the following risk factors: age ≥65 years, diabetes mellitus on medication, prior spontaneous MAI, multivessel CAD, or chronic renal dysfunction with eGFR <60 mL/min) who have tolerated dual antiplatelet therapy without a bleeding complication, treatment with dual antiplatelet therapy in the form of ticagrelor 60 mg twice a day on top of aspirin for longer than 12 months may be considered for up to three years. • The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with aspirin and oral anticoagulation. • Oral treatment with β-blockers should be considered during hospital stay and continued thereafter in all patients without contraindications. • Oral treatment with β-blockers is indicated in patients with heart failure or left ventricular dysfunction, LVEF ≤40% unless contraindicated. • Intravenous β-blockers must be avoided in patients with hypotension or acute heart failure or AV block or severe bradycardia. • Intravenous β-blockers should be considered at the time of presentation in patients undergoing primary PCI without contraindications, with high blood pressure, tachycardia, and no signs of heart failure. • A fasting lipid profile must be obtained in all STEMI patients, as soon as possible after presentation. • It is recommended to initiate or continue high dose statins early after admission in all STEMI patients without contraindication or history of intolerance, regardless of initial cholesterol values and maintain it long-term. • An LDL-C goal of <1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline LDL-C is between 1.8 to 3.5 mmol/L (70 to 135 mg/dL) is recommended. • In patients with LDL-C >1.8 mmol/L (>70 mg/dL) despite a maximally tolerated statin dose who remain at high risk, further therapy to reduce LDL-C should be considered. • ACE inhibitors are indicated starting within the first 24 hours of STEMI in patients with evidence of heart failure, LV systolic dysfunction, diabetes or an anterior infarct. • An ARB, preferably valsartan, is an alternative to ACE inhibitors in patients with heart failure or LV systolic dysfunction, particularly those who are intolerant to ACE inhibitors. • ACE inhibitors should be considered in all patients in the absence of contraindications. • Aldosterone antagonists, e.g. eplerenone, are indicated in patients with an ejection fraction ≤40% and heart failure or diabetes, provided no renal failure or hyperkalemia.
American College of Cardiology/ American Heart Association: **Guideline on the**	Top 10 messages for the primary prevention of cardiovascular disease • The most important way to prevent atherosclerotic vascular disease, heart failure, and atrial fibrillation is to promote a healthy lifestyle throughout life. • A team-based care approach is an effective strategy for the prevention of

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Primary Prevention of Cardiovascular Disease (2019)[23]	cardiovascular disease. Clinicians should evaluate the social determinants of health that affect individuals to inform treatment decisions. • Adults who are 40 to 75 years of age and are being evaluated for cardiovascular disease prevention should undergo 10-year atherosclerotic cardiovascular disease (ASCVD) risk estimation and have a clinician–patient risk discussion before starting on pharmacological therapy, such as antihypertensive therapy, a statin, or aspirin. In addition, assessing for other risk-enhancing factors can help guide decisions about preventive interventions in select individuals, as can coronary artery calcium scanning. • All adults should consume a healthy diet that emphasizes the intake of vegetables, fruits, nuts, whole grains, lean vegetable or animal protein, and fish and minimizes the intake of trans fats, processed meats, refined carbohydrates, and sweetened beverages. For adults with overweight and obesity, counseling and caloric restriction are recommended for achieving and maintaining weight loss. • Adults should engage in at least 150 minutes per week of accumulated moderate-intensity physical activity or 75 minutes per week of vigorous-intensity physical activity. • For adults with type 2 diabetes mellitus, lifestyle changes, such as improving dietary habits and achieving exercise recommendations, are crucial. If medication is indicated, metformin is first-line therapy, followed by consideration of a sodium-glucose cotransporter 2 inhibitor or a glucagon-like peptide-1 receptor agonist. • All adults should be assessed at every healthcare visit for tobacco use, and those who use tobacco should be assisted and strongly advised to quit. • Aspirin should be used infrequently in the routine primary prevention of ASCVD because of lack of net benefit. • Statin therapy is first-line treatment for primary prevention of ASCVD in patients with elevated low-density lipoprotein cholesterol levels (≥190 mg/dL), those with diabetes mellitus, who are 40 to 75 years of age, and those determined to be at sufficient ASCVD risk after a clinician–patient risk discussion. • Nonpharmacological interventions are recommended for all adults with elevated blood pressure or hypertension. For those requiring pharmacological therapy, the target blood pressure should generally be <130/80 mm Hg. <u>Adults with Type 2 Diabetes Mellitus</u> • For all adults with T2DM, a tailored nutrition plan focusing on a heart-healthy dietary pattern is recommended to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors. • Adults with T2DM should perform at least 150 minutes per week of moderate-intensity physical activity or 75 minutes of vigorous-intensity physical activity to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors. • For adults with T2DM, it is reasonable to initiate metformin as first-line therapy along with lifestyle therapies at the time of diagnosis to improve glycemic control and reduce ASCVD risk. • For adults with T2DM and additional ASCVD risk factors who require glucose-lowering therapy despite initial lifestyle modifications and metformin, it may be reasonable to initiate a sodium-glucose cotransporter 2 (SGLT-2) inhibitor or a glucagon-like peptide-1 receptor (GLP-1R) agonist to improve glycemic control and reduce CVD risk. <u>Adults with high blood cholesterol</u> • In adults at intermediate risk (≥7.5% to <20% 10-year ASCVD risk), statin therapy reduces risk of ASCVD, and in the context of a risk discussion, if a decision is made for statin therapy, a moderate-intensity statin should be

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	recommended. • In intermediate risk (≥7.5% to <20% 10-year ASCVD risk) patients, LDL-C levels should be reduced by 30% or more, and for optimal ASCVD risk reduction, especially in patients at high risk (≥20% 10-year ASCVD risk), levels should be reduced by 50% or more. • In adults 40 to 75 years of age with diabetes, regardless of estimated 10-year ASCVD risk, moderate-intensity statin therapy is indicated. • In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL (≥4.9 mmol/L) or higher, maximally tolerated statin therapy is recommended. • In adults with diabetes mellitus who have multiple ASCVD risk factors, it is reasonable to prescribe high-intensity statin therapy with the aim to reduce LDL-C levels by 50% or more. • In intermediate-risk (≥7.5% to <20% 10-year ASCVD risk) adults, risk-enhancing factors favor initiation or intensification of statin therapy. • In intermediate-risk (≥7.5% to <20% 10-year ASCVD risk) adults or selected borderline-risk (5% to <7.5% 10-year ASCVD risk) adults in whom a coronary artery calcium score is measured for the purpose of making a treatment decision, AND o If the coronary artery calcium score is zero, it is reasonable to withhold statin therapy and reassess in five to 10 years, as long as higher-risk conditions are absent (e.g., diabetes, family history of premature CHD, cigarette smoking); o If coronary artery calcium score is one to 99, it is reasonable to initiate statin therapy for patients ≥55 years of age; o If coronary artery calcium score is 100 or higher or in the 75th percentile or higher, it is reasonable to initiate statin therapy. • In patients at borderline risk (5% to <7.5% 10-year ASCVD risk), in risk discussion, the presence of risk-enhancing factors may justify initiation of moderate-intensity statin therapy. <u>Adults with high blood pressure or hypertension</u> • In adults with elevated blood pressure (BP) or hypertension, including those requiring antihypertensive medications nonpharmacological interventions are recommended to reduce BP. These include: o weight loss; o a heart-healthy dietary pattern; o sodium reduction; o dietary potassium supplementation; o increased physical activity with a structured exercise program; and o limited alcohol. • In adults with an estimated 10-year ASCVD risk (ACC/AHA pooled cohort equations to estimate 10-year risk of ASCVD) of 10% or higher and an average systolic BP (SBP) of 130 mm Hg or higher or an average diastolic BP (DBP) of 80 mm Hg or higher, use of BP-lowering medications is recommended for primary prevention of CVD. • In adults with confirmed hypertension and a 10-year ASCVD event risk of 10% or higher, a BP target of less than 130/80 mm Hg is recommended. • In adults with hypertension and chronic kidney disease, treatment to a BP goal of less than 130/80 mm Hg is recommended. • In adults with T2DM and hypertension, antihypertensive drug treatment should be initiated at a BP of 130/80 mm Hg or higher, with a treatment goal of less than 130/80 mm Hg. • In adults with an estimated 10-year ASCVD risk <10% and an SBP of 140 mm Hg or higher or a DBP of 90 mm Hg or higher, initiation and use of BP-lowering medication are recommended.

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	• In adults with confirmed hypertension without additional markers of increased ASCVD risk, a BP target of less than 130/80 mm Hg may be reasonable. <u>Recommendations for treatment of tobacco use</u> • All adults should be assessed at every healthcare visit for tobacco use and their tobacco use status recorded as a vital sign to facilitate tobacco cessation. • To achieve tobacco abstinence, all adults who use tobacco should be firmly advised to quit. • In adults who use tobacco, a combination of behavioral interventions plus pharmacotherapy is recommended to maximize quit rates. • In adults who use tobacco, tobacco abstinence is recommended to reduce ASCVD risk. • To facilitate tobacco cessation, it is reasonable to dedicate trained staff to tobacco treatment in every healthcare system. • All adults and adolescents should avoid secondhand smoke exposure to reduce ASCVD risk. <u>Recommendations for aspirin use</u> • Low-dose aspirin (75 to 100 mg orally daily) might be considered for the primary prevention of ASCVD among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk. • Low-dose aspirin (75 to 100 mg orally daily) should not be administered on a routine basis for the primary prevention of ASCVD among adults >70 years of age. • Low-dose aspirin (75 to 100 mg orally daily) should not be administered for the primary prevention of ASCVD among adults of any age who are at increased risk of bleeding.
American Heart Association/American College of Cardiology/ Heart Failure Society of America: **2022 AHA/ACC /HFSA Guideline for the Management of Heart Failure (2022)[24]**	<u>Treatment of Stage A heart failure (HF)</u> • Hypertension should be controlled in accordance with guideline-directed medication therapy for hypertension to prevent symptomatic HF. (LoE: A) • In patients with type 2 diabetes and either established CVD or at high cardiovascular risk, SGLT-2 inhibitors should be used to prevent hospitalizations for HF. (LoE: A) • In the general population, healthy lifestyle habits such as regular physical activity, maintaining normal weight, healthy dietary patterns, and avoiding smoking are helpful to reduce future risk of HF. (LoE: B) • Patients at risk of developing HF, natriuretic peptide biomarker-based screening followed by team-based care, including a cardiovascular specialist optimizing therapy, can be useful to prevent the development of LV dysfunction (systolic or diastolic) or new-onset HF. (LoE: B) <u>Treatment of Stage B heart failure</u> • In patients with LVEF≤40%, ACE inhibitors should be used to prevent HF and reduce mortality. (LoE: A) • In patients with a recent or remote history of MI or ACS, statins should be used to prevent symptomatic HF and adverse cardiovascular events. (LoE: A) • In patients with a recent MI and LVEF≤40% who are intolerant to ACE inhibitors, ARB should be used to prevent symptomatic HF and reduce mortality. (LoE: B) • In patients with a recent or remote history of MI or ACS and LVEF≤40%, evidence-based beta blockers should be used to reduce mortality. (LoE: B) • In patients who are at least 40 days post-MI with LVEF ≤30% and NYHA class I symptoms while receiving guideline-directed medication therapy and have reasonable expectation of meaningful survival for greater than one year, an

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	implantable cardioverter-defibrillator is recommended for primary prevention of sudden cardiac death to reduce total mortality. (LoE: B) • In patients with LVEF ≤40%, beta blockers should be used to prevent symptomatic HF. (LoE: C) • In patients with LVEF ≤50%, thiazolidinediones should not be used because they increase the risk of HF, including hospitalizations. (LoE: B) • In patients with LVEF ≤50%, nondihydropyridine calcium channel blockers with negative inotropic effects may be harmful. (LoE: C) <u>Treatment for Stage C Heart Failure with Reduced Ejection Fraction (HFrEF)</u> • For patients with stage C HF, avoiding excessive sodium intake is reasonable to reduce congestive symptoms. (LoE: C) • In patients with HF who have fluid retention, diuretics are recommended to relieve congestion, improve symptoms, and prevent worsening HF. (LoE: B) • For patients with HF and congestive symptoms, addition of a thiazide (e.g., metolazone) to treatment with a loop diuretic should be reserved for patients who do not respond to moderate or high dose loop diuretics to minimize electrolyte abnormalities. (LoE: B) • In patients with HFrEF and NYHA class II to III symptoms, the use of an ARNI is recommended to reduce morbidity and mortality. (LoE: A) • In patients with previous or current symptoms of chronic HFrEF, the use of an ACE inhibitor is beneficial to reduce morbidity and mortality when the use of an ARNI is not feasible. (LoE: A) • In patients with previous or current symptoms of chronic HFrEF, who are intolerant to an ACE inhibitor because of cough or angioedema, and when the use of an ARNI is not feasible, the use of an ARB is recommended to reduce morbidity and mortality. (LoE: A) • In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality. (LoE: B) • ARNIs should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor. (LoE: B) • ARNI or ACE inhibitors should not be administered in patients with a history of angioedema. (LoE: C) • In patients with HFrEF, with current or previous symptoms, use of one of the three β-blockers proven to reduce mortality (e.g., bisoprolol, carvedilol, sustained-release metoprolol succinate) is recommended to reduce mortality and hospitalizations. (LoE: A) • In patients with HFrEF and NYHA class II to IV symptoms, a mineralocorticoid receptor antagonist (spironolactone or eplerenone) is recommended to reduce morbidity and mortality, if eGFR is >30 mL/min/1.73 m^2 and serum potassium is <5.0 mEq/L. Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely followed thereafter to minimize risk of hyperkalemia and renal insufficiency. (LoE: A) • In patients taking a mineralocorticoid receptor antagonist whose serum potassium cannot be maintained at <5.5 mEq/L, mineralocorticoid receptor antagonist should be discontinued to avoid life threatening hyperkalemia. (LoE: B) • In patients with symptomatic chronic HFrEF, SGLT-2 an inhibitor is recommended to reduce hospitalization for HF and cardiovascular mortality, irrespective of the presence of type 2 diabetes. (LoE: A) • The combination of hydralazine and isosorbide dinitrate is recommended to improve symptoms and reduce morbidity and mortality for patients self-identified as African Americans with NYHA class III to IV HFrEF receiving optimal therapy. (LoE: A)

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	• In patients with current or previous symptomatic HFrEF who cannot be given first-line agents, such as an ARNI, ACE inhibitor or ARB because of drug intolerance or renal insufficiency, a combination of hydralazine and isosorbide dinitrate might be considered to reduce morbidity and mortality. (LoE: C) • In patients with HF class II to IV symptoms, omega-3 polyunsaturated fatty acid supplementation may be reasonable to use as adjunctive therapy to reduce mortality and cardiovascular hospitalizations. (LoE: B) • In patients with chronic HFrEF without specific indication (e.g., venous thromboembolism, atrial fibrillation, a previous thromboembolic event, or a cardioembolic source, anticoagulation is not recommended. (LoE: B) • Dihydropyridine and non-dihydropyridine calcium channel blockers are not recommended for patients with HFrEF. (LoE: A) • In patients with HFrEF, vitamins, nutritional supplements, and hormonal therapy are not recommended other than to correct specific deficiencies. (LoE: B) • In patients with HFrEF, class IC antiarrhythmic medication and dronedarone may increase risk of mortality. (LoE: A) • In patients with HFrEF, thiazolidinediones increase the risk of worsening HF symptoms and hospitalizations. (LoE: A) • In patients with type 2 diabetes and high cardiovascular risk, the DPP-4 inhibitors, saxagliptin and alogliptin, increase the risk of HF hospitalization and should be avoided in patients with HF. (LoE: B) • In patients with HFrEF, nonsteroidal anti-inflammatory drugs worsen HF symptoms and should be avoided or withdrawn whenever possible. (LoE: B) • For patients with symptomatic (NYHA class II to III) stable chronic HFrEF (LVEF ≤35%) who are receiving guideline-directed medical therapy, including a maximally tolerated dose of a beta blocker, and who are in sinus rhythm with a heart rate of ≥70 beats per minute at rest, ivabradine can be beneficial to reduce HF hospitalizations and cardiovascular death. (LoE: B) • In patients with symptomatic HFrEF despite guideline-directed medical therapy or who are unable to tolerate guideline-directed medical therapy, digoxin might be considered to decrease hospitalizations for HF. (LoE: B) • In select high-risk patients with HFrEF and recent worsening of HF already on guideline-directed medical therapy, an oral soluble guanylate cyclase stimulator (vericiguat) may be considered to reduce HF hospitalization and cardiovascular death. (LoE: B) <u>Pharmacological treatment for Stage C HF with mildly reduced EF and improved EF</u> • In patients with HF with mildly reduced EF, SGLT-2 inhibitors can be beneficial in decreasing HF hospitalizations and cardiovascular mortality. (LoE: B) • Among patients with current or previous symptomatic HF with mildly reduced EF (LVEF, 41 to 49%), use of evidence-based beta blockers for HFrEF, ARNI, ACE inhibitor or ARB, and mineralocorticoid receptor antagonists may be considered to reduce the risk of HF hospitalization and cardiovascular mortality, particularly among patients with LVEF on the lower end of this spectrum. (LoE: B) • In patients with HF with improved EF after treatment, guideline-directed medical therapy should be continued to prevent relapse of HF and LV dysfunction, even in patients who may become asymptomatic. (LoE: B) <u>Pharmacological treatment for Stage C HF with preserved EF (HFpEF)</u> • Patients with hypertension and HFpEF should have medication titrated to attain blood pressure targets in accordance with published clinical practice guidelines to prevent morbidity. (LoE: C) • SGLT-2 inhibitors can be beneficial in decreasing HF hospitalizations and cardiovascular mortality. (LoE: B)

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	• In patients with HFpEF, the use of a mineralocorticoid receptor antagonist, ARB, or ARNI may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum. (LoE: B) • Routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or quality of life in patients with HFpEF is ineffective. (LoE: B) <u>Treatment of Stage D (advanced/refractory) HF</u> • For patients with advanced HF and hyponatremia, the benefit of fluid restriction to reduce congestive symptoms is uncertain. (LoE: C) • Continuous intravenous inotropic support is reasonable as "bridge therapy" in patients with HF (Stage D) refractory to guideline-directed medical therapy and device therapy who are eligible for and awaiting mechanical circulatory support or cardiac transplantation. (LoE: B) • In select patients with HF Stage D, despite optimal guideline-directed medical therapy and device therapy who are ineligible for either mechanical circulatory support or cardiac transplantation, continuous intravenous inotropic support may be considered as palliative therapy for symptom control and improvement in functional status. (LoE: B) • Long-term use of either continuous or intermittent, intravenous inotropic agents, for reasons other than palliative care or as a bridge to advanced therapies, is potentially harmful. (LoE: B)
European Society of Cardiology: **Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (2021)**[25]	<u>Pharmacological treatments indicated in patients with (NYHA Class II-IV) heart failure with reduced ejection fraction</u> • An ACE inhibitor is recommended, in addition to a β-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death. • A mineralocorticoid receptor antagonist (MRA) is recommended for patients with HFrEF, who remain symptomatic despite treatment with an ACE inhibitor and a β-blocker, to reduce the risk of HF hospitalization and death. • Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death. Dapagliflozin or empagliflozin are recommended, in addition to optimal medical therapy with an ACE-I/ARNI, a β-blocker and an MRA, for patients with HFrEF regardless of diabetes status. • Sacubitril-valsartan is recommended as a replacement for an ACE inhibitor to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE inhibitor, a β-blocker, and a mineralocorticoid receptor antagonist. • Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion. • Ivabradine should be considered to reduce the risk of HF hospitalization or cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm despite treatment with an evidence-based dose of β-blocker (or maximum tolerated dose below that), ACE inhibitor (or ARB), and a mineralocorticoid receptor antagonist (or ARB). • Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm who are unable to tolerate or have contraindications for a β-blocker. Patients should also receive an ACE inhibitor (or ARB) and a mineralocorticoid receptor antagonist (or ARB). • An ARB is recommended to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients unable to tolerate an ACE inhibitor (patients should also receive a β-blocker and mineralocorticoid receptor antagonist). • An ARB may be considered to reduce the risk of HF hospitalization and death in patients who are symptomatic despite treatment with a β-blocker who are unable

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	to tolerate a mineralocorticoid receptor antagonist. • Vericiguat may be considered in patients in NYHA class II-IV who have had worsening HF despite treatment with an ACE-I (or ARNI), a β-blocker and an MRA to reduce the risk of CV mortality or HF hospitalization. • Hydralazine and isosorbide dinitrate should be considered in self-identified black patients with LVEF ≤35% or with an LVEF <45% combined with a dilated LV in NYHA Class III–IV despite treatment with an ACE-I a β-blocker and a mineralocorticoid receptor antagonist to reduce the risk of HF hospitalization and death. • Hydralazine and isosorbide dinitrate may be considered in symptomatic patients with HFrEF who can tolerate neither an ACE inhibitor nor an ARB (or they are contraindicated) to reduce the risk of death. • Digoxin is a treatment with less-certain benefits and may be considered in symptomatic patients in sinus rhythm despite treatment with an ACE inhibitor (or ARB), a β-blocker and a mineralocorticoid receptor antagonist, to reduce the risk of hospitalization (both all-cause and HF-hospitalizations). <u>Recommendations for treatment of patients with (NYHA class II-IV) heart failure with mildly reduced ejection fraction (HFmrEF)</u> • Diuretics are recommended in patients with congestion and HFmrEF in order to alleviate symptoms and signs. • An ACE inhibitor may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • An ARB may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • A β-blocker may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • An MRA may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • Sacubitril/valsartan may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. <u>Recommendations for treatment of patients with heart failure with preserved ejection fraction (HFpEF)</u> • It is recommended to screen patients with HFpEF for both cardiovascular and noncardiovascular comorbidities, which, if present, should be treated provided safe and effective interventions exist to improve symptoms, well-being and/or prognosis. • Diuretics are recommended in congested patients with HFpEF in order to alleviate symptoms and signs. <u>Recommendations for the primary prevention of heart failure in patients with risk factors for its development</u> • Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life. • Treatment with statins is recommended in patients at high risk of CV disease or with CV disease in order to prevent or delay the onset of HF, and to prevent HF hospitalizations. • SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with diabetes at high risk of CV disease or with CV disease in order to prevent HF hospitalizations. • Counselling against sedentary habit, obesity, cigarette smoking, and alcohol abuse is recommended to prevent or delay the onset of HF.

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	Recommendations for the initial management of patients with acute heart failure – pharmacotherapy • Intravenous loop diuretics are recommended for all patients with acute HF admitted with signs/symptoms of fluid overload to improve symptoms. It is recommended to regularly monitor symptoms, urine output, renal function and electrolytes during use of intravenous diuretics. • Combination of a loop diuretic with thiazide type diuretic should be considered in patients with resistant oedema who do not respond to an increase in loop diuretic doses. • In patients with acute HF and SBP >110 mmHg, intravenous vasodilators may be considered as initial therapy to improve symptoms and reduce congestion. • Inotropic agents may be considered in patients with SBP <90 mmHg and evidence of hypoperfusion who do not respond to standard treatment, including fluid challenge, to improve peripheral perfusion and maintain end-organ function. • Inotropic agents are not recommended routinely, due to safety concerns, unless the patient has symptomatic hypotension and evidence of hypoperfusion. • A vasopressor, preferably norepinephrine, may be considered in patients with cardiogenic shock to increase blood pressure and vital organ perfusion. • Thromboembolism prophylaxis (e.g. with LMWH) is recommended in patients not already anticoagulated and with no contraindication to anticoagulation, to reduce the risk of deep venous thrombosis and pulmonary embolism. • Routine use of opiates is not recommended, unless in selected patients with severe/intractable pain or anxiety.
Eighth Joint National Committee (JNC 8): **2014 Evidence-based Guideline for the Management of High Blood Pressure in Adults (2014)**[26]	• Pharmacologic treatment should be initiated in patients ≥60 years of age to lower blood pressure at systolic blood pressure ≥150 mm Hg or diastolic blood pressure ≥90 mm Hg and to a goal systolic blood pressure <150 mm Hg and goal diastolic blood pressure <90 mm Hg. Adjustment of treatment is not necessary if treatment results in lower blood pressure and treatment is well tolerated and without adverse effects on health or quality of life. • In patients <60 years of age, pharmacologic treatment should be initiated to lower blood pressure at diastolic blood pressure ≥90 mm Hg to a goal diastolic blood pressure <90 mm Hg. • In patients <60 years of age, pharmacologic treatment should be initiated to lower blood pressure at systolic blood pressure ≥150 mm Hg to a goal diastolic blood pressure <140 mm Hg. • For patients ≥18 years of age with chronic kidney disease or diabetes, pharmacologic treatment should be initiated to lower blood pressure at systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg and to a goal systolic blood pressure <140 mm Hg and goal diastolic blood pressure <90 mm Hg. • Initial antihypertensive treatment for the general nonblack population, including those with diabetes, should include thiazide-type diuretic, calcium channel blocker (CCB), ACE inhibitor, or ARB. • Initial antihypertensive treatment for the general black population, including those with diabetes, should include thiazide-type diuretic or CCB. • For patients ≥18 years of age with chronic kidney disease regardless of race or diabetes status, initial (or add-on) treatment should include an ACE inhibitor or ARB to improve kidney outcomes. • The main goal of antihypertensive treatment is to attain and maintain goal blood pressure. • If goal blood pressure is not attained within a month of treatment, the dose of the initial drug should be increased or second drug from the thiazide-type diuretic, CCB, ACE inhibitor, or ARB classes should be added. • If goal is not achieved with two drugs, a third drug from the thiazide-type diuretic,

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	CCB, ACE inhibitor, or ARB classes should be added. • An ACE inhibitor and ARB should not be used together. • Antihypertensive classes can be used if the patient is unable to achieve goal blood pressure with three agents or had a contraindication to a preferred class. • If blood pressure is not able to be achieved or in complicated patients, referral to a hypertension specialist may be indicated.
International Society of Hypertension: **Global Hypertension Practice Guidelines (2020)**[27]	<u>Lifestyle modifications</u> • Lifestyle modification is the first line of antihypertensive treatment. • Salt reduction: Reduce salt added when preparing foods, and at the table. Avoid or limit consumption of high salt foods such as soy sauce, fast foods and processed food including breads and cereals high in salt. • Healthy diet: Eating a diet that is rich in whole grains, fruits, vegetables, polyunsaturated fats and dairy products and reducing food high in sugar, saturated fat and trans fats, such as the DASH diet. • Healthy drinks: Moderate consumption of coffee, green and black tea. Other beverages that can be beneficial include karkadé (hibiscus) tea, pomegranate juice, beetroot juice and cocoa. • Moderation of alcohol consumption: The recommended daily limit for alcohol consumptions is 2 standard drinks for men and 1.5 for women (10 g alcohol/standard drink). Avoid binge drinking. • Weight reduction: Body weight control is indicated to avoid obesity. Particularly abdominal obesity should be managed. Ethnic-specific cut-offs for BMI and waist circumference should be used. Alternatively, a waist-to-height ratio <0.5 is recommended for all populations. • Smoking cessation: Smoking is a major risk factor for cardiovascular disease (CVD), COPD and cancer. Smoking cessation and referral to smoking cessation programs are advised. • Regular physical activity: Studies suggest that regular aerobic and resistance exercise may be beneficial for both the prevention and treatment of hypertension. Moderate intensity aerobic exercise (walking, jogging, cycling, yoga, or swimming) for 30 minutes on five to seven days per week Strength training also can help reduce blood pressure. Performance of resistance/strength exercises on two to three days per week. • Reduce stress and induce mindfulness: Stress should be reduced and mindfulness or meditation introduced into the daily routine. • Reduce exposure to air pollution and cold temperature: Evidence from studies support a negative effect of air pollution on blood pressure in the long-term. <u>Pharmacological Treatment</u> • Ideal characteristics of drug treatment o Treatments should be evidence-based in relation to morbidity/mortality prevention. o Use a once-daily regimen which provides 24-hour blood pressure control. o Treatment should be affordable and/or cost-effective relative to other agents. o Treatments should be well-tolerated. o Evidence of benefits of use of the medication in populations to which it is to be applied. • General scheme for drug treatment o Lifestyle modification is the first line of antihypertensive treatment. o Grade 1 hypertension (BP 140 to 159/ 90 to 99): Immediate drug treatment in high-risk patients or those with CVD, chronic kidney disease (CKD), diabetes mellitus (DM), or hypertension-mediated organ damage (HMOD). Drug treatment after three to six months of lifestyle

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	intervention if BP still not controlled in low to moderate risk patients. o Grade 2 hypertension (BP ≥160/100): Immediated drug treatment in all patients. • Core drug-treatment strategy o Step 1: Dual low-dose combination (ACE inhibitor or ARB plus dihydropyridine-calcium channel blockers (DHP-CCB)); consider monotherapy in low-risk grade 1 hypertension or in very old (≥80 years) or frail patients; consider ACE/ARB plus thiazide-like diuretic in post-stroke, very elderly, incipient HF, or CCB intolerance; consider ACE/ARB plus DHP-CCB or DHP-CCB plus thiazide-like diuretics in black patients. o Step 2: Dual full-dose combination (ACE inhibitor or ARB plus DHP-CCB); consider monotherapy in low-risk grade 1 hypertension or in very old (≥80 years) or frail patients; consider ACE/ARB plus thiazide-like diuretic in post-stroke, very elderly, incipient HF, or CCB intolerance. o Step 3: Triple combination (ACE/ARB plus DHP-CCB plus thiazide-like diuretic). o Step 4, resistant hypertension: triple combination plus spironolactone or other drug, alternatives include amiloride, doxazosin, eplerenone, clonidine, or β-blocker. Caution with spironolactone or other potassium sparing diuretics when estimated GFR <45 mL/min/1.73m^2 or K+ >4.5 mmol/L. o Consider β-blockers at any treatment step when there is a specific indications for their use, e.g., heart failure, angina, post-MI, atrial fibrillation, or younger women planning pregnancy or pregnant.
Hypertension Canada: **2020 Guidelines for the Prevention, Diagnosis, Risk Assessment, and Treatment of Hypertension in Adults and Children (2020)**[28]	<u>Indications for drug therapy for adults with hypertension without compelling indications for specific agents</u> • Antihypertensive therapy should be prescribed for average diastolic blood pressure (DBP) measurements of ≥100 mmHg or average systolic blood pressure (SBP) measurements of ≥160 mmHg in patients without macrovascular target organ damage or other cardiovascular risk factors. • Antihypertensive therapy should be strongly considered for average DPB readings ≥90 mmHg or for average SBP readings ≥140 mmHg in the presence of macrovascular target organ damage or other independent cardiovascular risk factors. • For high-risk patients, aged 50 years or older, with SBP levels ≥130 mmHg, intensive management to target a SBP <120 mmHg should be considered. Patient selection for intensive management is recommended and caution should be taken in certain high-risk groups. <u>Indications for drug therapy for adults with diastolic and with or without systolic hypertension</u> • Initial therapy should be with either monotherapy or single pill combination (SPC). o Recommended monotherapy choices are: ▪ A thiazide/thiazide-like diuretic, with longer-acting diuretics preferred; ▪ A β-blocker (in patients <60 years of age); ▪ An angiotensin-converting enzyme (ACE) inhibitor (in nonblack patients); ▪ An angiotensin receptor blocker (ARB); or ▪ A long-acting calcium channel blocker (CCB). o Recommended SPC choices are those in which an ACE inhibitor is combined with a CCB, ARB with a CCB, or ACE inhibitor or ARB with a diuretic. o Hypokalemia should be avoided in patients treated with thiazide/thiazide-like

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	diuretic monotherapy. • Additional antihypertensive drugs should be used if target BP levels are not achieved with standard-dose monotherapy. Add-on drugs should be chosen from first-line choices. Useful choices include a thiazide/thiazide-like diuretic or CCB with either: ACE inhibitor, ARB, or β-blocker. Caution should be exercised in combining a nondihydropyridine CCB and a β-blocker. The combination of an ACE inhibitor and an ARB is not recommended. • If BP is still not controlled with a combination of two or more first-line agents, or there are adverse effects, other antihypertensive drugs may be added. • Possible reasons for poor response to therapy should be considered. • α-Blockers are not recommended as first-line agents for uncomplicated hypertension; β-blockers are not recommended as first-line therapy for uncomplicated hypertension in patients ≥60 years of age; and ACE inhibitors are not recommended as first-line therapy for uncomplicated hypertension in black patients. However, these agents may be used in patients with certain comorbid conditions or in combination therapy. <u>Indications for drug therapy for adults with isolated systolic hypertension</u> • Initial therapy should be single-agent therapy with a thiazide/thiazide-like diuretic, a long-acting dihydropyridine CCB, or an ARB. If there are adverse effects, another drug from this group should be substituted. Hypokalemia should be avoided in patients treated with thiazide/thiazide-like diuretic monotherapy. • Additional antihypertensive drugs should be used if target BP levels are not achieved with standard-dose monotherapy. Add-on drugs should be chosen from first-line options. • If BP is still not controlled with a combination of two or more first-line agents, or there are adverse effects, other classes of drugs (such as α-blockers, ACE inhibitors, centrally acting agents, or nondihydropyridine CCBs) may be combined or substituted. • Possible reasons for poor response to therapy should be considered. • α-Blockers are not recommended as first-line agents for uncomplicated isolated systolic hypertension; and β-blockers are not recommended as first-line therapy for isolated systolic hypertension in patients ≥60 years of age. However, both agents may be used in patients with certain comorbid conditions or in combination therapy. <u>Guidelines for hypertensive patients with coronary artery disease (CAD)</u> • For most hypertensive patients with CAD, an ACE inhibitor or ARB is recommended. • For hypertensive patients with CAD, but without coexisting systolic heart failure, the combination of an ACE inhibitor and ARB is not recommended. • For high-risk hypertensive patients, when combination therapy is being used, choices should be individualized. The combination of an ACE inhibitor and a dihydropyridine CCB is preferable to an ACE inhibitor and a thiazide/thiazide-like diuretic in selected patients. • For patients with stable angina pectoris but without previous heart failure, myocardial infarction, or coronary artery bypass surgery, either a β-blocker or CCB can be used as initial therapy. • Short-acting nifedipine should not be used. • When decreasing SBP to target levels in patients with established CAD (especially if isolated systolic hypertension is present), be cautious when the DBP is ≤60 mmHg because of concerns that myocardial ischemia might be exacerbated, especially in patients with left ventricular hypertrophy (LVH). <u>Guidelines for patients with hypertension who have had a recent myocardial infarction</u>

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	• Initial therapy should include a β-blocker as well as an ACE inhibitor.
	• An ARB can be used if the patient is intolerant of an ACE inhibitor.
	• CCBs may be used in patients after myocardial infarction when β-blockers are contraindicated or not effective. Nondihydropyridine CCBs should not be used when there is heart failure, evidenced by pulmonary congestion on examination or radiography.
	
	<u>Treatment of hypertension in association with heart failure</u>
	• In patients with systolic dysfunction (ejection fraction <40%), ACE inhibitors and β-blockers are recommended for initial therapy. Aldosterone antagonists (mineralocorticoid receptor antagonists) may be combined in treatment for patients with a recent cardiovascular hospitalization, acute myocardial infarction, elevated B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide level, or New York Heart Association (NYHA) Class II-IV symptoms. Careful monitoring for hyperkalemia is recommended when combining an aldosterone antagonist with ACE inhibitor or ARB treatment. Other diuretics are recommended as additional therapy if needed. Beyond considerations of BP control, doses of ACE inhibitors or ARBs should be titrated to those reported to be effective in trials unless adverse effects become manifest.
	• An ARB is recommended if ACE inhibitors are not tolerated.
	• A combination of hydralazine and isosorbide dinitrate is recommended if ACE inhibitors and ARBs are contraindicated or not tolerated.
	• For hypertensive patients whose BP is not controlled, an ARB may be combined with an ACE inhibitor and other antihypertensive drug treatment. Careful monitoring should be used if combining an ACE inhibitor and an ARB because of potential adverse effects such as hypotension, hyperkalemia, and worsening renal function. Additional therapies may also include dihydropyridine CCBs.
	• An angiotensin receptor-neprilysin inhibitor (ARNI) should be used in place of an ACE inhibitor or ARB for patients with HFrEF (<40%) who remain symptomatic despite treatment with appropriate dose of guideline directed HF therapy. Eligible patients must have a serum potassium <5.2 mmol/L, an eGFR ≤30 mL/min/1.73m^2 and close surveillance of serum potassium and creatinine.
	
	<u>Treatment of hypertension in association with stroke</u>
	• BP management in acute ischemic stroke (onset to 72 hours)
	  ○ Please refer to Stroke Best Practice recommendations.
	• BP management after acute ischemic stroke
	  ○ Strong consideration should be given to the initiation of antihypertensive therapy after the acute phase of a stroke or transient ischemic attack.
	  ○ After the acute phase of a stroke, BP-lowering treatment is recommended to a target of consistently <140/90 mmHg.
	  ○ Treatment with an ACE inhibitor and thiazide/thiazide-like diuretic combination is preferred.
	  ○ For patients with stroke, the combination of an ACE inhibitor and ARB is not recommended.
	• BP management in hemorrhagic stroke (onset to 72 hours)
	  ○ Please refer to Stroke Best Practice recommendations.
	
	<u>Treatment of hypertension in association with LVH</u>
	• Hypertensive patients with LVH should be treated with antihypertensive therapy to decrease the rate of subsequent cardiovascular events.
	• The choice of initial therapy can be influenced by the presence of LVH. Initial therapy can be drug treatment using ACE inhibitors, ARBs, long-acting CCBs, or thiazide/thiazide-like diuretics. Direct arterial vasodilators such as hydralazine or minoxidil should not be used.

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	Treatment of hypertension in association with nondiabetic chronic kidney disease • Individualize BP targets in patients with chronic kidney disease. Consider intensive targets (SBP <120 mmHg) in appropriate patients. • For patients with hypertension and proteinuric chronic kidney disease (urinary protein >150 mg per 24 hours or albumin to creatinine ratio >30 mg/mmol), initial therapy should be an ACE inhibitor or an ARB if there is intolerance to ACE inhibitors. • In most cases, combination therapy with other antihypertensive agents might be needed to reach target BP levels. • The combination of an ACE inhibitor and ARB is not recommended for patients with nonproteinuric chronic kidney disease. Treatment of hypertension in association with renovascular disease • Patients with hypertension attributable to atherosclerotic renal artery stenosis should be primarily medically managed because renal angioplasty and stenting offers no benefit over optimal medical therapy alone. • Renal artery angioplasty and stenting for atherosclerotic hemodynamically significant renal artery stenosis could be considered for patients with uncontrolled hypertension resistant to maximally tolerated pharmacotherapy, progressive renal function loss, and acute pulmonary edema. • Patients with confirmed renal fibromuscular dysplasia (FMD) should be referred to a hypertension specialist. • Renal artery angioplasty without stenting is recommended for treatment of FMD-related renal artery stenosis. Stenting is not recommended unless needed because of a periprocedural dissection. Surgical revascularization should be considered in cases of complex lesions less amendable to angioplasty, stenosis associated with complex aneurysm, and restenosis despite two unsuccessful attempts of angioplasty. Treatment of hypertension in association with diabetes mellitus • Persons with diabetes mellitus should be treated to attain SBP of <130 mmHg and DBP of <80 mmHg. • For persons with cardiovascular or kidney disease, including microalbuminuria, or with cardiovascular risk factors in addition to diabetes and hypertension, an ACE inhibitor or an ARB is recommended as initial therapy. • For persons with diabetes and hypertension not included in other guidelines in this section, appropriate choices include (in alphabetical order): ACE inhibitors, ARBs, dihydropyridine CCBs, and thiazide/thiazide-like diuretics. • If target BP levels are not achieved with standard-dose monotherapy, additional antihypertensive therapy should be used. For persons in whom combination therapy with an ACE inhibitor is being considered, a dihydropyridine CCB is preferable to a thiazide/thiazide-like diuretic. Resistant hypertension • Resistant hypertension is defined as BP above target despite three or more BP-lowering drugs at optimal doses preferably including a diuretic (and usually a renin-angiotensin-aldosterone system blocker and a CCB. • Accurate office and out-of-office BP measurement is essential. • Other reasons for apparent resistant hypertension should be eliminated before diagnosing true resistant hypertension, including nonadherence, white coat effect, and secondary hypertension. • Pharmacotherapy with the additional use of spironolactone, bisoprolol, doxazosin, amiloride, eplerenone, or clonidine with the baseline regimen decreases BP

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	significantly, with the greatest BP-lowering shown with spironolactone. • Patients with resistant hypertension should be referred to providers with expertise in diagnosis and management of hypertension. <u>Hypertension and pediatrics</u> • BP should be measured regularly in children three years of age or older; the auscultatory method is the gold-standard at present. • Initial therapy should be monotherapy, with an ACE inhibitor or ARB (not first-line in black children), or a long-acting dihydropyridine CCB. • The treatment t goal is systolic and diastolic office BP and/or ABPM < 95th percentile or <90th percentile in children with risk factors or target organ damage. • Complex cases should be referred to an expert in pediatric hypertension. <u>Hypertension and pregnancy</u> • Up to 7% of pregnancies are complicated by a hypertensive disorder of pregnancy, and approximately 5% of women will have chronic hypertension when they become pregnant. • The prevalence of hypertension in pregnancy is expected to increase with women becoming pregnant later in their reproductive years and the increasing prevalence of cardiovascular comorbidities such as increased preconception body mass index and maternal diabetes. • The possibility of pregnancy should be considered when managing women with hypertension who are of reproductive age. • Preconception counselling should be offered to all women with hypertension who are considering pregnancy. • ACE inhibitor and ARB therapy should be avoided before conception and during pregnancy unless there is a compelling indication for their use (i.e., proteinuric kidney disease). • Hypertension during pregnancy can increase the risk of adverse maternal and fetal outcomes, including an increased risk of preeclampsia, placental abruption, prematurity, small for gestational age infants, stillbirth, and maternal renal and retinal injury, thus generally requires involvement of an interdisciplinary team including obstetrical care providers. • Antihypertensive therapy is recommended for average SBP measurements of ≥140 mmHg or DBP measurements of ≥90 mmHg in pregnant women with chronic hypertension, gestational hypertension, or preeclampsia. Initial antihypertensive therapy should be monotherapy from the following first-line drugs: oral labetalol, oral methyldopa, long-acting oral nifedipine, or other oral b-blockers (acebutolol, metoprolol, pindolol, and propranolol). Other antihypertensive drugs can be considered as second-line drugs including: clonidine, hydralazine, and thiazide diuretics. • Women with severe hypertension with SBP ≥160 mmHg or DBP ≥110 mmHg in pregnancy or postpartum require urgent antihypertensive therapy because it is considered an obstetrical emergency. • Antihypertensive drugs used in breastfeeding women include: labetalol, methyldopa, long-acting nifedipine, enalapril, or captopril.
European Society of Hypertension: **2023 Guidelines for the management of arterial hypertension (2023)**[29]	<u>General recommendations for antihypertensive drug treatment</u> • BP lowering should be prioritized over the selection of specific antihypertensive drug classes because treatment benefit largely originates from BP reduction. • Five major drug classes including, ACE inhibitors, ARBs, β-blockers, CCBs, and Thiazide/Thiazide-like diuretics have effectively reduced blood pressure and cardiovascular events in randomized controlled trials. These drugs and their combinations are recommended as the basis of antihypertensive treatment strategies.

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	• Initiation of therapy with a two-drug combination is recommended for most hypertensive patients. Preferred combinations should comprise a RAS blocker (either an ACE inhibitor or an ARB) with a CCB or thiazide/thiazide-like diuretic. Other combinations of the five major drug classes can be used. • Initiation with monotherapy can be considered in patients with: grade 1 hypertension and low-risk if BP is only marginally elevated (less than 150 mmHg SBP and 95 mmHg DBP) high-normal BP and very high cardiovascular risk, frailty and/or and advance age. • If BP is not controlled with the initial two-drug combination by using the maximum recommended and tolerated dose of the respective components, treatment should be increased to a three-drug combination, usually a RAS blocker plus CCB plus thiazide/thiazide-like diuretic. • If BP is not controlled with a three-drug combination by using the maximum recommended and tolerated dose of the respective components, it is recommended to extend treatment according to the recommendations for resistant hypertension. • The use of single pill combinations should be preferred at any treatment step (i.e. during initiation of therapy with a two-drug combination and at any other step of treatment). • β-blocker should be used at initiation of therapy or at any treatment step as guideline-directed medical therapy (e.g., heart failure with reduced ejection fraction, anti-ischemic therapy in chronic coronary syndromes, heart rate control in atrial fibrillation). • β-blockers can be considered in the presence of several other conditions in which their use can be favorable. • The combination of two RAS blockers is not recommended due to increased risk of adverse events, in particular AKI. <u>True-resistant hypertension</u> • In resistant hypertension, it is recommended to reinforce lifestyle measures. • Drugs that can be considered as additional therapy in patients with resistant hypertension are preferably spironolactone (or other MRA), or β-blocker or Alpha-1 blockers or centrally acting agents (clonidine), or amiloride. • Thiazide/thiazide-like diuretics are recommended in resistant hypertension if estimated eGFR is ≥30 mL/min/1.73m^2. • Loop diuretics may be considered in patients with an estimated eGFR < 45 mL/min/1.73m^2 and should be used if eGFR falls below 30 mL/min/1.73m^2. • Chlorthalidone (12.5 to 25 mg once daily) could be used with or without a loop diuretic if eGFR is <30 mL/min/1.73m^2. • Renal deprivation can be considered as an additional treatment option in patients with resistant hypertension if eGFR is >40 mL/min/1.73m^2. • Patients with resistant hypertension should be followed very closely. Follow-up includes periodical ambulatory blood pressure monitoring and assessment of hypertension-mediated organ damage, particularly kidney function and serum potassium levels. Regular use of home blood pressure monitoring and monitoring of drug adherence are desirable.
National Institute for Health and Clinical Excellence: **Hypertension in adults: diagnosis and management (2019)**[30]	<u>Choosing antihypertensive drug treatment (for people with or without type II diabetes)</u> • Where possible, recommend treatment with drugs taken only once a day. • Prescribe non-proprietary drugs where these are appropriate and minimize cost. • Offer people with isolated systolic hypertension (systolic blood pressure ≥160 mmHg) the same treatment as people with both raised systolic and diastolic blood pressure. • Offer antihypertensive drug treatment to women of child-bearing potential with diagnosed hypertension in line with recommendations in this guideline. For

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	women considering pregnancy or who are pregnant or breastfeeding, manage hypertension in line with the recommendations on Management of pregnancy with chronic hypertension and Breastfeeding in 'Hypertension in pregnancy'. • When choosing antihypertensive drug treatment for adults of black African or African-Caribbean family origin, consider an angiotensin II receptor blocker, in preference to an angiotensin-converting enzyme inhibitor. <u>Step one treatment</u> • Patients <55 years of age should be offered a step one antihypertensive with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). • Offer an ACE inhibitor or an ARB to adults starting step 1 antihypertensive treatment who have type II diabetes and are of any age or family origin or those aged <55 years but not of black African or African-Caribbean family origin. • If an ACE inhibitor is not tolerated, offer an ARB. • Do not combine an ACE inhibitor with an ARB for the treatment of hypertension. • Offer a calcium channel blocker (CCB) to adults starting step 1 antihypertensive treatment who are >55 years of age and do not have diabetes and are of black African or African-Caribbean family origin and do not have type II diabetes and of any age. • If a CCB is not suitable, for example because of edema or intolerance, or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic. • If diuretic treatment is to be initiated or changed, offer a thiazide‑like diuretic, such as indapamide in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide. • For adults with hypertension who are already receiving treatment with bendroflumethiazide or hydrochlorothiazide, who have stable, well-controlled blood pressure, continue with their treatment. <u>Step two treatment</u> • Before considering next step treatment for hypertension discuss with the person if they are taking their medicine as prescribed and support adherence in line with NICE's guideline on “Medicines adherence: involving patients decisions about prescribed medicines and supporting adherence”. • If hypertension is not controlled with a step one treatment of an ACE inhibitor or ARB, offer choice of one of the following drugs in addition to the step one treatment: a CCB or a thiazide-like diuretic. • If hypertension is not controlled in adults taking step one treatment of a CCB, offer the choice of one of the following drugs in addition to the step one treatment: an ACE inhibitor or an ARB or a thiazide-like diuretic. • If hypertension is not controlled in adults of black African or African–Caribbean family origin who do not have type 2 diabetes taking step one treatment, consider an ARB, in preference to an ACE inhibitor, in addition to step one treatment. <u>Step three treatment</u> • Before considering step three treatment, review the person’s medications to ensure they are being taken at the optimal doses and discuss adherence (see recommendation under step two). • If hypertension is not controlled in adults taking step two treatment, offer a combination of an ACE inhibitor or ARB and a CCB and a thiazide-like diuretic. <u>Step four treatment</u> • If hypertension is not controlled in adults taking the optimal tolerated doses of an

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	ACE inhibitor or an ARB plus a CCB and a thiazide-like diuretic, regard them as having resistant hypertension. • Before considering further treatment for a person with resistant hypertension, confirm elevated clinic blood pressure measurements using ambulatory or home blood pressure recordings, assess for postural hypotension, and discuss adherence. • For people with confirmed resistant hypertension, consider adding a fourth antihypertensive drug as step four treatment or seeking specialist advice. • Consider further diuretic therapy with low-dose spironolactone for adults with resistant hypertension starting step four treatment who have a blood potassium level of 4.5 mmol/l or less. Use particular caution in people with a reduced estimated glomerular filtration rate because they have an increased risk of hyperkalemia. • When using further diuretic therapy for step four treatment of resistant hypertension, monitor blood sodium and potassium and renal function within one month of starting treatment and repeat as needed thereafter. • Consider an alpha-blocker or beta-blocker for adults with resistant hypertension starting step four treatment who have a blood potassium level of more than 4.5 mmol/l. • If blood pressure remains uncontrolled in people with resistant hypertension taking the optimal tolerated doses of four drugs, seek specialist advice.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in Blacks (2010)**[31]	• To attain and maintain blood pressure (BP) below target levels, multiple antihypertensive drugs will be required in most hypertensive blacks. • Use of two-drug combination therapy when SBP is >15 mm Hg and/or DBP is >10 mm Hg above goal levels is increasingly recommended as first-line therapy. • Two-drug regimens have generally contained a thiazide-type diuretic; however, the combination of a calcium channel blocker (CCB) with either an ACE inhibitor or an ARB has been shown equally efficacious in BP lowering but with demonstrated superiority (CCB+ACE) for hard clinical outcomes compared with the same ACE inhibitor plus a thiazide-type diuretic. • In secondary prevention patients, the combination therapy should include a drug(s) with the appropriate compelling indications. • Certain classes of antihypertensive medications, specifically diuretics and CCBs, lower BP on average more than β-blockers and renin-angiotensin system (RAS) blockers in black patients when used as monotherapies. • In the absence of compelling indications, when BP is near goal levels, monotherapy with a diuretic or a CCB is preferred. • Lifestyle modifications should be initiated in all patients with hypertension, whether or not pharmacotherapy is planned. • ACE inhibitors or ARBs are recommended as alternative monotherapy options in the treatment of hypertension in blacks. The rationale for their lower tier monotherapy recommendation is because they have consistently achieved lesser average reductions in BP relative to that observed with monotherapy using either a diuretic or CCB.
Kidney Disease Improving Clinical Outcomes Group: **KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease (2021)**[32]	<u>Blood pressure measurement</u> • The Work Group recommends standardized office blood pressure (BP) measurement in preference to routine office BP measurements for the management of high BP in adults. • The Work Group suggests that out-of-office BP measurements with ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM) be used to complement standardized office BP readings for the management of high BP. <u>Lifestyle interventions for lowering BP in patients with chronic kidney disease (CKD) not receiving dialysis</u>

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	• The Work Group suggests targeting a sodium intake <2 grams of sodium per day (or <90 mmol of sodium per day, or <5 grams of sodium chloride per day) in patients with high BP and CKD. • The Work Group suggests that patients with high BP and CKD be advised to undertake moderate-intensity physical activity for a cumulative duration of at least 150 minutes per week, or to a level compatible with their cardiovascular and physical tolerance. BP management in patients with CKD, with or without diabetes, not receiving dialysis • The Work Group suggests that adults with high BP and CKD be treated with a target systolic BP (SBP) of <120 mmHg, when tolerated, using standardized office BP measurement. • The Work Group recommends starting renin-angiotensin-system inhibitors (RASi) (angiotensin-converting enzyme inhibitor [ACEi] or angiotensin II receptor blocker [ARB]) for people with high BP, CKD, and severely increased albuminuria without diabetes. • The Work Group suggests starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately increased albuminuria without diabetes. • The Work Group recommends starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately-to-severely increased albuminuria with diabetes. • The Work Group recommends avoiding any combination of ACEi, ARB, and direct renin inhibitor (DRI) therapy in patients with CKD, with or without diabetes. BP management in kidney transplant recipients • Treat adult kidney transplant recipients with high BP to a target BP of <130 mmHg systolic and <80 mmHg diastolic using standardized office BP measurement. • The Work Group recommends that a dihydropyridine calcium channel blocker (CCB) or an ARB be used as the first-line antihypertensive agent in adult kidney transplant recipients. BP management in children with CKD • The Work Group suggests that in children with CKD, 24-hour mean arterial pressure by ABPM should be lowered to <50th percentile for age, sex, and height.
American Diabetes Association: **Standards of Medical Care in Diabetes (2023)**[33]	Hypertension/blood pressure control • Blood pressure should be measured at every routine visit. When possible, patients found to have elevated blood pressure (systolic blood pressure 120 to 129 mmHg and diastolic <80 mmHg) should have blood pressure confirmed using multiple readings, including measurements on a separate day, to diagnose hypertension. Patients with blood pressure ≥180/110 and cardiovascular disease could be diagnosed with hypertension at a single visit. • All hypertensive patients with diabetes should monitor their blood pressure at home. • For patients with diabetes and hypertension, blood pressure targets should be individualized through a shared decision-making process that addresses cardiovascular risk, potential adverse effects of antihypertensive medications, and patient preferences. • Individuals with diabetes and hypertension qualify for antihypertensive drug therapy when the blood pressure is persistently elevated ≥130/80 mmHg. The on-treatment target blood pressure goal is <130/80 mmHg, if it can be safely attained. • In pregnant patients with diabetes and preexisting hypertension, a blood pressure target of 110 to 135/85 is suggested in the interest of reducing the risk for accelerated maternal hypertension and minimizing impaired fetal growth.

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	• For patients with blood pressure >120/80, lifestyle intervention consists of weight loss when indicated, a Dietary Approaches to Stop Hypertension (DASH)-style eating pattern including reducing sodium and increasing potassium intake, moderation of alcohol intake, and increased physical activity. • Patients with confirmed office-based blood pressure ≥130/80 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of pharmacologic therapy to achieve blood pressure goals. • Patients with confirmed office-based blood pressure ≥160/100 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of two drugs or a single pill combination of drugs demonstrated to reduce cardiovascular events in patients with diabetes. • Treatment for hypertension should include drug classes demonstrated to reduce cardiovascular events in patients with diabetes (ACE inhibitors, angiotensin receptor blockers, thiazide-like diuretics, or dihydropyridine calcium channel blockers). ACE inhibitors or angiotensin receptor blockers are recommended first-line therapy for hypertension in people with diabetes and coronary artery disease. • Multiple-drug therapy is generally required to achieve blood pressure targets (but not a combination of ACE inhibitors and angiotensin receptor blockers). • An ACE inhibitor or angiotensin receptor blocker, at the maximum tolerated dose indicated for blood pressure treatment, is the recommended first-line treatment for hypertension in patients with diabetes and urinary albumin–to–creatinine ratio ≥300 mg/g creatinine or 30 to 299 mg/g creatinine. If one class is not tolerated, the other should be substituted. • For patients treated with an ACE inhibitor, angiotensin receptor blocker, or diuretic, serum creatinine/estimated glomerular filtration rate and serum potassium levels should be monitored at least annually. • Patients with hypertension who are not meeting blood pressure targets on three classes of antihypertensive medications (including a diuretic) should be considered for mineralocorticoid receptor antagonist therapy. <u>Chronic kidney disease</u> • At least once a year, assess urinary albumin (e.g., spot urinary albumin–to–creatinine ratio) and estimated glomerular filtration rate in patients with type 1 diabetes with duration of five or more years and in all patients with type 2 diabetes. • In people with established diabetic kidney disease, urinary albumin (e.g., spot urinary albumin-to-creatinine ratio) and estimated glomerular filtration rate should be monitored one to four times per year depending on the stage of the disease. Optimize glucose control to reduce the risk or slow the progression of chronic kidney disease (CKD). • For patients with type 2 diabetes and diabetic kidney disease, use of a sodium-glucose cotransporter 2 inhibitor in patients with an estimated glomerular filtration rate ≥20 mL/min/1.73 m^2 and urinary albumin ≥200 mg/g creatinine is recommended to reduce CKD progression and cardiovascular events. • For patients with type 2 diabetes and diabetic kidney disease, use of a sodium–glucose cotransporter 2 inhibitor is recommended to reduce chronic kidney disease progression and cardiovascular events in patients with an estimated glomerular filtration rate ≥20 mL/min/1.73 m^2 and urinary albumin ranging from normal to 200 mg/g creatinine. • In people with type 2 diabetes and diabetic kidney disease, consider use of sodium–glucose cotransporter 2 inhibitors (if estimated glomerular filtration rate is ≥20 mL/min/1.73 m^2), a glucagon-like peptide 1 agonist, or a nonsteroidal mineralocorticoid receptor antagonist (if estimated glomerular filtration rate is ≥25 mL/min/1.73 m^2) additionally for cardiovascular risk reduction. • In people with chronic kidney disease and albuminuria who are at increased risk

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	for cardiovascular events or chronic kidney disease progression, a nonsteroidal mineralocorticoid receptor antagonist shown to be effective in clinical trials is recommended to reduce chronic kidney disease progression and cardiovascular events. • Optimize blood pressure control and reduce blood pressure variability to reduce the risk or slow the progression of CKD. • Do not discontinue renin-angiotensin system blockade for minor increases in serum creatinine (≤30%) in the absence of volume depletion. • For people with nondialysis-dependent stage 3 or higher CKD, dietary protein intake should be a maximum of 0.8 g/kg body weight per day (the recommended daily allowance). For patients on dialysis, higher levels of dietary protein intake should be considered, since protein energy wasting is a major problem in some dialysis patients. • In nonpregnant patients with diabetes and hypertension, either an ACE inhibitor or an angiotensin receptor blocker is recommended for those with modestly elevated urinary albumin–to–creatinine ratio (30 to 299 mg/g creatinine) and is strongly recommended for those with urinary albumin–to–creatinine ratio ≥300 mg/g creatinine and/or estimated glomerular filtration rate <60 mL/min/1.73 m^2. • Periodically monitor serum creatinine and potassium levels for the development of increased creatinine and hyperkalemia when ACE inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists are used, or hypokalemia when diuretics are used. • An ACE inhibitor or an angiotensin receptor blocker is not recommended for the primary prevention of CKD in patients with diabetes who have normal blood pressure, normal urinary albumin–to–creatinine ratio (<30 mg/g creatinine), and normal estimated glomerular filtration rate. • Patients should be referred for evaluation by a nephrologist if they have continuously increasing urinary albumin levels and/or continuously decreasing estimated glomerular filtration rate and an estimated glomerular filtration rate <30 mL/min/1.73 m^2. • Promptly refer to a nephrologist for uncertainty about the etiology of kidney disease, difficult management issues, and rapidly progressing kidney disease.
American College of Cardiology/American Heart Association Task Force: **Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults (2017)**[34]	<u>Initiation of Blood Pressure (BP) Treatment for Overall Cardiovascular Disease (CVD) Risk</u> • Use of BP-lowering medications is recommended for secondary prevention of recurrent CVD events in patients with clinical CVD and an average systolic blood pressure (SBP) ≥130 mmHg or an average diastolic blood pressure (DBP) of ≥80 mmHg and for primary prevention in adults with an estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk of ≥10% and an average SBP of ≥130 mmHg or an average ≥80 mmHg. • Use of BP-lowering medication is recommended for primary prevention of CVD in adults with no history of CVD and with an estimated 10-year ASCVD risk <10% and an SBP of ≥140 mmHg or a DBP of ≥90 mmHg. • Simultaneous use of an angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), and/or renin inhibitor is potentially harmful and is not recommended to treat adults with hypertension. • For adults with confirmed hypertension and known CVD or 10-year ASCVD risk of ≥10%, a BP target <130/80 mmHg is recommended. For adults with confirmed hypertension without additional markers of increased CVD risk, a BP target <130/80 mmHg may be reasonable. • For initiation of antihypertensive drug therapy, first-line agents include thiazide diuretics, calcium channel blockers (CCBs), and ACE inhibitors or ARBs. • Initiation of antihypertensive drug therapy with two first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended

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	in adults with stage 2 hypertension and an average BP >20/10 mmHg above their BP target. • Initiation of antihypertensive drug therapy with a single antihypertensive drug is reasonable in adults with stage 1 hypertension and BP goal <130/80 mmHg with dosage titration and sequential addition of other agents to achieve the BP target. Stable Ischemic Heart Disease (SIHD) • In adults with SIHD and hypertension, a BP target <130/80 is recommended. • Adults with SIHD and hypertension (BP ≥130/80 mmHg) should be treated with medications [e.g., guideline-directed medical therapy (GDMT) beta-blockers, ACE inhibitors, or ARBs] for compelling indications [e.g., previous myocardial infarction (MI), stable angina] as first-line therapy, with the addition of other drugs (e.g., dihydropyridine CCBs, thiazide diuretics, and/or mineralocorticoid receptor antagonists) as needed to further control hypertension. • In adults with SIHD with angina and persistent uncontrolled hypertension, the addition of dihydropyridine CCBs to GDMT beta-blockers is recommended. • In adults who have had a MI or acute coronary syndrome, it is reasonable to continue GDMT beta-blockers beyond three years as long-term therapy for hypertension. • Beta-blockers and/or CCBs might be considered to control hypertension in patients with coronary artery disease (CAD) had an MI more than three years ago and have angina. Heart Failure • In adults with increased risk of HF, the optimal BP in those with hypertension should be <130 mmHg. • Adults with HFrEF and hypertension should be prescribed GDMT titrated to attain a BP <130/80 mmHg. • Non-dihydropyridine CCBs are not recommended in the treatment of hypertension in adults with HFrEF. • In adults with HFpEF who present with symptoms of volume overload, diuretics should be prescribed to control hypertension. • Adults with HFpEF and persistent hypertension after management of volume overload should be prescribed ACE inhibitors or ARBs and beta-blockers titrated to attain SBP <130 mmHg. CKD • Adults with hypertension and CKD should be treated to a BP goal <130/80 mmHg. • In adults with hypertension and CKD [stage 3 or higher or stage 1 or 2 with albuminuria (≥300 mg/d, or ≥300 mg/g albumin-to-creatinine ratio or the equivalent in the first morning void)], treatment with an ACE inhibitor is reasonable to slow kidney disease progression. Treatment with an ARB may be reasonable if an ACE inhibitor is not tolerated. • After kidney transplantation, it is reasonable to treat patients with hypertension to a BP goal <130/80 mmHg and with a CCB on the basis of improved glomerular filtration rate (GFR) and kidney survival. Cerebrovascular Disease • In adults with intracerebral hemorrhage (ICH) who present with SBP >220 mmHg, it is reasonable to use continuous intravenous (IV) drug infusion and close BP monitoring to lower levels. Immediate lowering of SBP to <140 mmHg in adults with spontaneous ICH who present within six hours of the acute event and have an SBP between 150 mmHg and 220 mmHg is not of benefit to reduce death or severe disability and can be potentially harmful.

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	• Adults with acute ischemic stroke and elevated BP who are eligible for treatment with IV tissue plasminogen activator (tPA) should have their BP slowly lowered to <185/110 mmHg before thrombolytic therapy is initiated. • In adults with an acute ischemic stroke, BP should be <185/110 mmHg before administration of IV tPA and should be maintained below 180/105 mmHg for at least the first 24 hours after initiation drug therapy. • Starting or restarting antihypertensive therapy during hospitalization in patients with BP >140/90 mmHg who are neurologically stable is safe and reasonable to improve long-term BP control, unless contraindicated. • In patient with BP ≥220/120 mmHg who did not receive IV alteplase or endovascular treatment and have no comorbid conditions requiring acute antihypertensive treatment, the benefit of initiating or reinitiating treatment of hypertension within the first 48 to 72 hours is uncertain. It might be reasonable to lower BP by 15% during the first 24 hours after onset of stroke. In patients with BP <220/120 mmHg with the same conditions, initiating or reinitiating treatment of hypertension within the first 48 to 72 hours after an acute ischemic stroke is not effective to prevent death or dependency. • Adults with previously treated stroke or transient ischemic attack should be restarted on antihypertensive treatment after the first few days of the index event to reduce the risk of recurrent stroke and other vascular events. Treatment with a thiazide diuretic, ACE inhibitor, or ARB, or combination treatment consisting of a thiazide diuretic plus ACE inhibitor, is useful. • Adults not previously treated for hypertension who experienced a stroke or transient ischemic attack and have an established BP ≥140/90 mmHg should be prescribed antihypertensive treatment a few days after the index event to reduce the risk of recurrent stroke and other vascular event. • For adults who experience a stroke or transient ischemic attack, selection of specific drugs should be individualized on the basis of patient comorbidities and agent pharmacological class. • For adults who experience a stroke or transient ischemic attack, a BP goal <130/80 mmHg may be reasonable. • For adults with a lacunar stroke, a target SBP goal <130 mmHg may be reasonable. • In adults previously untreated for hypertension who experience an ischemic stroke or transient ischemic attack and have an SBP <140 mmHg and a DBP <90 mmHg, the usefulness of initiating antihypertensive treatment is not well established. <u>Peripheral Artery Disease (PAD)</u> • Adults with hypertension and PAD should be treated similarly to patients with hypertension without PAD. <u>Diabetes Mellitus (DM)</u> • In adults with DM and hypertension, antihypertensive drug treatment should be initiated at a BP of ≥130/80 mmHg with a treatment goal <130/80 mmHg. • In adults with DM and hypertension, all first-line classes of antihypertensive agents (i.e., diuretics, ACE inhibitors, ARBs, and CCBs) are useful and effective. • In adults with DM and hypertension, ACE inhibitors or ARBs may be considered in the presence of albuminuria. <u>Atrial Fibrillation, Valvular Heart Disease, and Aortic disease</u> • Treatment of hypertension can be useful for prevention of recurrence of AF. • In adults with asymptomatic aortic stenosis, hypertension should be treated with pharmacotherapy, starting at a low dose and gradually titrating upward as needed. • In patients with chronic aortic insufficiency, treatment of systolic hypertension

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	with agents that do not slow the heart rate (i.e., avoid beta-blockers) is reasonable. • Beta-blockers are recommended as the preferred antihypertensive agents in patients with hypertension and thoracic aortic disease. Racial and Ethnic Differences in Treatment • In black adults with hypertension but without HF or CKD, including those with DM, initial antihypertensive treatment should include a thiazide-type diuretic or CCB. Two or more antihypertensive medications are recommended to achieve a BP target <130/80 mmHg in most adults with hypertension, especially in black adults with hypertension. Pregnancy • Women with hypertension who become pregnant, or are planning to become pregnant, should be transitioned to methyldopa, nifedipine, and/or labetalol during pregnancy. • Women with hypertension who become pregnant should not be treated with ACE inhibitors, ARBs, or direct renin inhibitors. Older Persons • Treatment of hypertension with an SBP treatment goal <130 mmHg is recommended for noninstitutionalized ambulatory community-dwelling adults (≥65 years of age) with an average SBP of ≥130 mmHg. • For older adults (≥65 years of age) with hypertension and a higher burden of comorbidity and limited life expectancy, clinical judgment, patient preference, and a team-based approach to assess risk/benefit is reasonable for decisions regarding intensity of BP lowering and choice of antihypertensive drugs. Hypertensive Crises • In adults with a hypertensive emergency, admission to an intensive care unit is recommended for continuous monitoring of BP and target organ damage and for parenteral administration of an appropriate agent. • For adults with a compelling condition (i.e., aortic dissection, severe pre-eclampsia or eclampsia, or pheochromocytoma crisis), SBP should be reduced to <140 mmHg during the first hour and to <120 mmHg in aortic dissection. • For adults without a compelling condition, SBP should be reduced by no more than 25% within the first hours; then, if stable, to 160/100 mmHg within the next two to six hours; and then cautiously to normal during the following 24 to 48 hours. Cognitive Decline and Dementia • In adults with hypertension, BP lowering is reasonable to prevent cognitive decline and dementia. Patients Undergoing Surgical Procedures • In patients with hypertension undergoing major surgery who have been on beta-blockers chronically, beta-blockers should be continued. • In patients with hypertension undergoing planned elective major surgery, it is reasonable to continue medical therapy for hypertension until surgery. • In patients with hypertension undergoing major surgery, discontinuation of ACE inhibitors or ARBs perioperatively may be considered. • In patients with planned elective major surgery and SBP ≥180 mmHg or DBP ≥110 mmHg, deferring surgery may be considered. • For patients undergoing surgery, abrupt pre-operative discontinuation of beta-blockers or clonidine is potentially harmful.

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	• Beta-blockers should not be started on the day of surgery in beta-blocker-naïve patients. • Patients with intraoperative hypertension should be managed with IV medications until such time as oral medications can be resumed.

*Agent not available in the United States.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the dihydropyridines are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Dihydropyridines[1,5-17]

Indication(s)	Single Entity Agents								Combination Products			
	Amlodipine	Felodipine	Isradipine	Levamlodipine	Nicardipine	Nifedipine	Nimodipine	Nisoldipine	Amlodipine and Benazepril	Amlodipine and Olmesartan	Amlodipine and Valsartan	Amlodipine and Valsartan and HCTZ
Angina Pectoris												
Treatment of chronic stable angina	✔ *				✔ (IR)†							
Treatment of chronic stable angina without evidence of vasospasm in patients who remain symptomatic despite adequate doses of β-blockers and/or organic nitrates or who cannot tolerate those agents						✔ (capsule)						
Treatment of vasospastic angina	✔ ‡					✔ (capsule, ER tablet)§						
Coronary Artery Disease (CAD)												
Reduce the risk of hospitalization due to angina and to reduce the risk of a coronary revascularization procedure in patients with recently documented CAD by angiography and without heart failure or an ejection fraction <40%	✔											
Hypertension												
Treatment of hypertension	✔ ‖	✔ ‖	✔ ¶	✔ ‖	✔ ‖ #	✔ (ER)‖		✔ ‖	✔ **	✔ ‖	✔ ††	✔ ‡‡
Miscellaneous												
Improvement of neurological outcome by reducing the incidence and severity of ischemic deficits in patients with subarachnoid hemorrhage from ruptured intracranial berry aneurysms regardless of their post-ictus neurological condition (i.e., Hunt and Hess Grades I-V)							✔					

*Alone or in combination with other antianginal agents.
†Alone or in combination with β-blockers.

‡Confirmed or suspected vasospastic angina. Alone or may be used in combination with other antianginal agents.
§Vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm.
‖Alone or in combination with other antihypertensive agents.
¶Alone or in combination with thiazide-type diuretics.
#Cardene IV® is indicated for the short term treatment of hypertension when oral therapy is not feasible or not desirable. For prolonged control of blood pressure, transfer patients to oral medication as soon as their clinical condition permits.
**Not adequately controlled on monotherapy with either agent
††Not adequately controlled on monotherapy or as initial therapy in patients likely to need multiple drugs to achieve their blood pressure goals
‡‡This fixed combination drug is not indicated for the initial therapy of hypertension.
ER=extended-release, IR=immediate-release

IV. Pharmacokinetics

The pharmacokinetic parameters of the dihydropyridines are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Dihydropyridines[2]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Amlodipine	64 to 90	93	Liver, extensive	Renal (70)	30 to 60
Felodipine	13 to 20	>99	Liver, extensive	Renal (70) Feces (10)	26.7 to 33.2
Isradipine	14 to 24 IR: 90 to 95 CR: 15 to 24	95	Liver, complete	Renal (60 to 65) Feces (25 to 30)	8
Levamlodipine	64 to 90	93	Liver, extensive	Renal (60% metabolites, 10% unchanged)	30 to 50
Nicardipine	35	>95	Liver, nearly 100%	Oral: Renal (60) Feces (35) IV with oral dose: Renal (49) Feces (43 within 96 hours)	IV: 14.4 Oral: 8.6
Nifedipine	IR: rapid and complete ER: complete	92 to 98	Liver, extensive	Renal (80) Feces (20)	2
Nimodipine	13	>95	Liver, extensive	Renal (<1) Feces (% not reported)	1 to 2
Nisoldipine	5	>99	Liver, extensive	Renal (60 to 80) Feces (6 to 12)	13.7 ± 4.3
Combination Products					
Amlodipine and benazepril	64 to 90/≥37	93/93	Liver, extensive (% not reported)/ Liver, extensive (% not reported)	Renal (60% inactive, 10% unchanged)/ Renal (20)	48/ 10 to 11
Amlodipine and olmesartan	64 to 90/26	93/99	Liver, extensive (90)/ Intestinal wall (100)	Renal (10)/ Renal (35 to 50) Feces (50 to 65)	45/7
Amlodipine and valsartan	64 to 90/25	93/95	Liver, extensive (90)/ Not reported	Renal (60)/ Renal (13) Feces (83)	30 to 50/ 6
Amlodipine and valsartan and HCTZ	64 to 90/ 25/ 60 to 80	93/ 95/ 40	Liver, extensive (90)/ Liver, minimal (20)/ Not metabolized	Renal (60)/ Renal (7 to 13) Feces (83)/ Renal (>61)	45/ 6 to 9/ 5.8 to 18.9

CR=controlled-release, ER=extended-release, HCTZ=hydrochlorothiazide, IR=immediate-release

V. Drug Interactions

Major drug interactions with the dihydropyridines are listed in Table 5.

Table 5. Major Drug Interactions with the Dihydropyridines[2]

Generic Name(s)	Interaction	Mechanism
ARBs (olmesartan, valsartan)	Potassium-sparing diuretics	The risk of hyperkalemia may be increased when potassium-sparing diuretics are co-administered with ACE inhibitors or ARBs.
Amlodipine, levamlodipine	Simvastatin	Simvastatin plasma concentrations may be elevated, increasing the risk of toxicity (e.g., myositis, rhabdomyolysis).
ACE inhibitors (benazepril)	Aldosterone blockers	Serious hyperkalemia, possibly with cardiac arrhythmias or arrest, may occur with the combination of aldosterone blockers and benazepril.
ACE inhibitors (benazepril)	Immunosuppressants (Azathioprine and Mercaptopurine	Concurrent use of immunosuppressants and benazepril may result in myelosuppression.
ACE inhibitors (benazepril)	Sacubitril	Concurrent use of sacubitril and ACE inhibitors may result in increased risk of angioedema.
ACE inhibitors (benazepril)	Potassium-sparing diuretics	The risk of hyperkalemia may be increased when potassium-sparing diuretics are co-administered with ACE inhibitors or ARBs.
Dihydropyridines (amlodipine, felodipine, isradipine, levamlodipine, nifedipine, nimodipine, nisoldipine)	Macrolide antibiotics	Inhibition of nifedipine metabolism (CYP3A4) by macrolide and related antibiotics may lead to elevated dihydropyridine plasma concentrations, increasing the pharmacologic effects and risk of adverse reactions (e.g., severe hypotension).
Dihydropyridines (amlodipine, levamlodipine)	Rifampin	Concurrent use of amlodipine and rifampin may result in reduced amlodipine efficacy.
Thiazide diuretics (HCTZ)	Dofetilide	Thiazide diuretics may induce hypokalemia which may increase the risk of torsades de pointes.
Thiazide diuretics (HCTZ)	Lithium	Thiazide diuretics may promote enhanced proximal tubular reabsorption of lithium leading to elevated serum concentrations. Thiazide diuretics may increase the therapeutic and toxic effects of lithium.
Dihydropyridines (felodipine, isradipine, nifedipine, nimodipine, nisoldipine)	Azole antifungals	Dihydropyridine serum levels may increase resulting from a decrease metabolism due to CYP3A4 inhibition by azole antifungal agents.
Dihydropyridines (amlodipine, levamlodipine, nimodipine)	HCV protease inhibitors	Dihydropyridine serum levels may increase resulting from a decrease metabolism due to CYP3A4 inhibition by protease inhibitors.
Dihydropyridines (amlodipine, levamlodipine, nifedipine, nimodipine)	HIV protease inhibitors	Dihydropyridine serum levels may increase resulting from a decrease metabolism due to CYP3A4 inhibition by protease inhibitors.
Dihydropyridines (nimodipine)	Barbiturates	Metabolism of dihydropyridines may be increased due to induction of mixed function oxidases by barbiturates, causing an increase in first-pass metabolism and decreased bioavailability, reducing the effects of dihydropyridines.
ARBs (olmesartan, valsartan)	Aliskiren	Concurrent use of aliskiren may result in an increased risk of hyperkalemia, renal impairment, and hypotension.
ARBs (olmesartan,	ACE Inhibitors	Coadministration of ARBs and ACE inhibitors may be

Generic Name(s)	Interaction	Mechanism
valsartan)		associated with an increased risk of renal dysfunction and/or hyperkalemia.
ARBs (olmesartan, valsartan)	Lithium	Elevations in plasma lithium levels may occur.
ARBs (olmesartan, valsartan)	Potassium preparations	Hyperkalemia, possibly with cardiac arrhythmias or cardiac arrest, may occur with the combination of olmesartan and potassium preparations.
Dihydropyridines (amlodipine, felodipine, isradipine, nicardipine, nifedipine, nisoldipine)	Clopidogrel	Concurrent use may result in decreased antiplatelet effect and increased risk of thrombotic events.
Dihydropyridines (isradipine)	Mefloquine	Concurrent use of isradipine and mefloquine may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
Dihydropyridines (nimodipine)	Hydantoins	Dihydropyridine serum levels may decrease due to increased first-pass metabolism caused by hydantoins.
ACE inhibitors (benazepril)	Aliskiren	The risk of hyperkalemia, renal impairment, and hypotension may be increased when aliskiren is coadministered with benazepril.
ACE inhibitors (benazepril)	mTOR inhibitors (everolimus and sirolimus)	The risk of angioedema may be increased with concurrent administration of mTOR inhibitors and benazepril.
ACE inhibitors (benazepril)	Alteplase	Concurrent use of alteplase and ACE inhibitors may result in an increased risk of orolingual angioedema.
ACE inhibitors (benazepril)	HIV protease inhibitors	Pharmacologic effects of benazepril may be increased by HIV protease inhibitors.
ACE inhibitors (benazepril)	Imidazoles	Imidazoles may increase the plasma concentrations and pharmacologic effects of benazepril.
ACE inhibitors (benazepril)	NSAIDs	The antihypertensive effects of benazepril may be decreased by NSAIDs. Nephrotoxicity associated with benazepril or NSAIDs may be increased by this drug combination.
ACE inhibitors (benazepril)	Lithium	Pharmacologic effects of lithium may be increased by benazepril. Elevated lithium serum concentrations with toxicity may occur.
ACE inhibitors (benazepril)	Potassium preparations	Hyperkalemia, possibly with cardiac arrhythmias or cardiac arrest, may occur with the combination of benazepril and potassium preparations.
ACE inhibitors (benazepril)	Trimethoprim	Hyperkalemia, possibly with cardiac arrhythmias or cardiac arrest, may occur with the combination of trimethoprim and benazepril.
ACE inhibitors (benazepril, felodipine, nimodipine)	Vasopressin receptor antagonists	Plasma concentrations of benazepril may be increased by co-administration of vasopressin receptor antagonists.
Dihydropyridines (isradipine)	Inhaled anesthetics	Concurrent use may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
Dihydropyridines (isradipine)	Phenothiazines	Concurrent use of isradipine and phenothiazines may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
Dihydropyridines (isradipine)	Tricyclic antidepressants	Concurrent use of isradipine and tricyclic antidepressants may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).

Generic Name(s)	Interaction	Mechanism
Dihydropyridines (amlodipine, felodipine, nicardipine)	Cyclosporine	Cyclosporine serum levels may increase due to inhibited metabolism by dihydropyridines.
Dihydropyridines (felodipine, nifedipine, nimodipine)	Carbamazepine	Carbamazepine may decrease plasma concentrations and effects of nifedipine.
Dihydropyridines (nicardipine, nifedipine)	Fentanyl	Concurrent use of fentanyl and nicardipine may result in severe hypotension.
Dihydropyridines (amlodipine, nicardipine, nifedipine)	Tacrolimus	Tacrolimus serum levels may be elevated due to inhibition of metabolism by dihydropyridines.
Thiazide diuretics (HCTZ)	Diazoxide	The combination of diazoxide with a thiazide diuretic may lead to hyperglycemia though an unknown mechanism; therefore, the combination should be avoided.
Thiazide diuretics (HCTZ)	Digitalis glycosides	Thiazide diuretics may induce electrolyte disturbances which may predispose patients to digitalis-induced arrhythmias.
Dihydropyridines (clevidipine, isradipine, nicardipine, nicardipine, nimodipine, nisoldipine)	Digitalis glycosides	Dihydropyridines may induce electrolyte disturbances which may predispose patients to digitalis-induced arrhythmias.
Calcium channel blockers (amlodipine, levamlodipine)	Digoxin	Concurrent use of digoxin and calcium channel blockers may result in increased risk of complete heart block.
Nimodipine	Rifapentine	Rifapentine can reduce plasma concentrations of nimodipine and reduce efficacy levels of nimodipine
Nimodipine	Dexamethasone	Dexamethasone can reduce plasma concentrations of nimodipine and reduce efficacy levels of nimodipine
Nimodipine	rifampin	Rifampin can reduce plasma concentrations of nimodipine and reduce efficacy levels of nimodipine
Nimodipine	Phenobarbital	Phenobarbital can reduce plasma concentrations of nimodipine and reduce efficacy levels of nimodipine
Nimodipine	Phenytoin	Phenytoin can reduce plasma concentrations of nimodipine and reduce efficacy levels of nimodipine
Nimodipine	Nefazodone	Nefazodone can increase serum nimodipine levels
Nimodipine	Delavirdine	Delavirdine can increase serum nimodipine levels.
Nicardipine	Vecuronium	The combination of vecuronium and nicardipine can result in enhanced neuromuscular blockade
Isradipine	Arsenic trioxide	The combination of arsenic trioxide and isradipine can result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
Isradipine	Zolmitriptan	The combination of zolmitriptan and isradipine can result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
Isradipine	Fluoxetine	The combination of fluoxetine and isradipine can result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
Isradipine	Octreotide	The combination of octreotide and isradipine can result in an increased risk of cardiotoxicity (QT prolongation, torsades de

Generic Name(s)	Interaction	Mechanism
		pointes, cardiac arrest)
Isradipine	Pentamidine	The combination of isradipine and pentamidine can result increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
Isradipine	Dolasetron, ondansetron	The combination of isradipine and dolasetron can increase the risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
Isradipine	Gemifloxacin	The combination of isradipine and Gemifloxacin can increase the risk of cardiotoxicity (QT prolongation, torsades de pointes cardiac arrest)
Dihydropyridines (felodipine, isradipine, nicardipine, nimodipine)	St. John's Wort	St. John's wort may reduce serum levels of dihydropyridines creating subtherapeutic levels of dihydropyridines for antihypertensive activity.
Calcium Channel Blockers (amlodipine, levamlodipine, felodipine, isradipine, nicardipine	Droperidol	Combination of droperidol and calcium channel blockers can increase risk of cardiotoxicity including QT prolongation, torsades de pointes, or cardiac arrest.
Felodipine	Nilotinib	The combination of nilotinib and felodipine can increase exposure of either felodipine or nilotinib.
Dihydropyridines (clevidipine, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine)	Lacosamide	The combination of dihydropyridines and lacosamide can result in prolonged PR interval, AV block, brady cardia, and ventricular tachyarrhythmia
Calcium Channel Blockers (clevidipine, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine)	Dantrolene	The combination of dantrolene and calcium channel blockers may result in hyperkalemia with cardiovascular collapse.

ACE inhibitors=angiotensin converting enzyme inhibitors, ARB=angiotensin II receptor blocker, CYP=cytochrome P450 isoenzyme, HCTZ=hydrochlorothiazide, HIV=human immunodeficiency virus, NSAID=nonsteroidal anti-inflammatory drug,

VI. Adverse Drug Events

The most common adverse drug events reported with the dihydropyridines are listed in Tables 6 and 7. The boxed warnings for the dihydropyridines are listed in Tables 8 through 12.

Table 6. Adverse Drug Events (%) Reported with the Dihydropyridines (Amlodipine-containing Products)[1,5-17]

Adverse Events	Single Entity Agents	Combination Products			
	Amlodipine, Levamlodipine	Amlodipine and Benazepril	Amlodipine and Olmesartan	Amlodipine and Valsartan	Amlodipine and Valsartan and HCTZ
Cardiovascular					
Arrhythmia	1	-	-	✔	-
Atrial fibrillation	1	-	-	1	-
Bradycardia	1	-	-	1	-
Cardiac murmur	-	-	-	✔	-
Chest pain	1	-	-	1	-

Adverse Events	Single Entity Agents	Combination Products			
	Amlodipine, Levamlodipine	Amlodipine and Benazepril	Amlodipine and Olmesartan	Amlodipine and Valsartan	Amlodipine and Valsartan and HCTZ
Edema	2 to 11	2	2 to 15	✔	7
Hypotension	-	-	✔	✔	-
Orthostatic hypotension	-	-	✔	<1	-
Palpitations	1 to 5	✔	1 to 5	✔	0.5
Peripheral ischemia	1	-	-	1	-
Peripheral edema	18 to 26	✔	✔	5	-
Pitting edema	-	-	-	✔	-
Postural dizziness	1	-	-	-	-
Postural hypotension	-	-	-	1	-
Pulse irregularity	-	-	-	✔	-
Syncope	1	-	-	-	-
Tachycardia	1	-	-	✔	✔
Vasculitis	1	-	-	1	-
Ventricular tachycardia	1	-	-	1	-
Central Nervous System					
Abnormal dreams	1	-	-	1	-
Agitation	1	-	-	✔	-
Amnesia	1	-	-	✔	-
Anxiety	-	✔	-	3	-
Apathy	1	-	-	✔	-
Asthenia	1	✔	✔	✔	-
Ataxia	-	-	-	✔	-
Carpal tunnel syndrome	-	-	-	✔	-
Cervicobrachial syndrome	-	-	-	✔	-
Depersonalization	1	-	-	1	-
Depression	1 to 2	-	-	✔	-
Dizziness	1 to 3	1	1 to 3	2	8
Headache	7	2	-	11	5
Hypoesthesia	1	-	-	✔	-
Insomnia	1	✔	-	✔	-
Migraine	-	-	-	✔	-
Nervousness	1	✔	-	1	-
Paresthesia	1	-	-	✔	-
Peripheral neuropathy	1	-	-	1	-
Postural dizziness	-	✔	-	1	<1
Pyrexia	-	-	-	✔	-
Sciatica	-	-	-	✔	-
Sinus headache	-	-	-	✔	-
Somnolence	<2	✔	<2	3	✔
Syncope	-	✔	-	1	✔
Tremor	1	✔	-	1	✔
Vertigo	1	-	-	✔	-
Dermatologic					
Alopecia	-	-	✔	✔	-
Cold and clammy skin	1	-	-	✔	-
Dermatitis	-	✔	-	✔	-
Eczema	-	-	-	✔	-
Erythema	-	-	-	✔	-
Erythema multiforme	1	-	-	1	-
Exanthema	-	-	-	✔	-
Flushing	1 to 3	✔	1 to 3	✔	-
Hyperhidrosis	1	-	-	✔	-
Pruritus	1	-	✔	✔	✔
Rash	1 to 2	✔	✔	✔	✔
Rash, erythematous	1 to 2	-	-	1	-
Rash, maculopapular	✔	-	-	1	-
Skin discoloration	1	-	-	✔	-
Skin dryness	1	-	-	✔	-
Urticaria	1	-	✔	✔	-
Endocrine and Metabolic					
Decreased libido	-	✔	-	-	-
Gout	-	-	-	✔	-
Gynecomastia	✔	-	✔	-	-

Adverse Events	Single Entity Agents	Combination Products			
	Amlodipine, Levamlodipine	Amlodipine and Benazepril	Amlodipine and Olmesartan	Amlodipine and Valsartan	Amlodipine and Valsartan and HCTZ
Diabetes mellitus	-	-	-	✔	-
Thirst	1	-	-	1	-
Gastrointestinal					
Abdominal discomfort	-	-	-	✔	-
Abdominal distension	-	-	-	✔	-
Abdominal pain	2	✔	-	3	-
Anorexia	1	-	-	1	-
Colitis	-	-	-	✔	-
Constipation	1	✔	-	✔	✔
Diarrhea	✔	✔	✔	3	✔
Dry mouth	✔	✔	-	✔	✔
Dyspepsia	1	-	-	✔	2
Dysphagia	1 to 2	-	-	1	-
Esophagitis	-	✔	-	-	-
Flatulence	1	-	-	✔	-
Gastritis	-	-	-	✔	✔
Gastroenteritis	-	-	-	✔	-
Hemorrhoids	-	-	-	✔	✔
Hepatitis	-	-	-	✔	-
Increased appetite	-	-	-	✔	-
Jaundice	✔	-	✔	✔	✔
Loose stools	1	-	-	✔	-
Nausea	3	✔	-	3	2
Pancreatitis	1	-	-	1	-
Sprue-like enteropathy	-	-	✔	-	-
Vomiting	1	-	✔	✔	-
Genitourinary					
Cystitis	-	-	-	✔	-
Dysuria	-	-	-	✔	-
Erectile dysfunction	-	-	-	✔	✔
Hematuria	-	-	-	✔	-
Impotence	-	✔	-	✔	-
Micturition disorder	1	-	-	1	-
Nephrolithiasis	-	-	-	✔	-
Nocturia	1	-	✔	1	-
Pollakiuria	-	-	-	✔	-
Polyuria	-	✔	-	✔	-
Sexual dysfunction	1 to 2	-	-	1	-
Urinary frequency	1	-	✔	✔	-
Urinary tract infection	-	-	-	✔	-
Hematological					
Leukopenia	1	-	-	1	-
Neutropenia	-	✔	-	✔	✔
Purpura	1	-	-	1	-
Thrombocytopenia	1	-	-	✔	-
Blood urea nitrogen increased	-	-	-	✔	✔
Creatinine increases	-	-	✔	✔	✔
Hepatic enzyme elevations	✔	-	✔	✔	✔
Hypercholesterolemia	-	-	-	✔	-
Hyperglycemia	1	-	-	1	-
Hyperkalemia	-	✔	✔	3 to 10	-
Hypokalemia	-	✔	-	-	-
Musculoskeletal					
Arthralgia	1	-	-	✔	✔
Arthrosis	1	-	-	1	-
Back pain	1 to 2	✔	-	✔	2
Hypertonia	-	-	-	✔	-
Joint sprain	-	-	-	✔	-
Joint swelling	-	-	-	✔	✔
Limb injury	-	-	-	✔	-
Malaise	1	-	-	1	-
Muscle cramps	1	✔	-	1	-
Muscle spasms	-	-	-	✔	2

Adverse Events	Single Entity Agents	Combination Products			
	Amlodipine, Levamlodipine	Amlodipine and Benazepril	Amlodipine and Olmesartan	Amlodipine and Valsartan	Amlodipine and Valsartan and HCTZ
Muscle weakness	-	-	-	✔	✔
Musculoskeletal chest pain	-	-	-	✔	-
Myalgia	1 to 2	✔	-	✔	-
Osteoarthritis	-	-	-	✔	✔
Pain	1	-	-	✔	-
Rhabdomyolysis	✔	-	✔	✔	-
Twitching	1	-	-	✔	-
Respiratory					
Bronchitis	-	-	-	✔	-
Cough	-	3	-	2	✔
Dysphonia	-	-	-	✔	-
Dyspnea	1	-	-	1	-
Epistaxis	1 to 2	-	-	✔	-
Influenza	-	-	-	2	-
Nasal congestion	-	-	-	✔	✔
Nasopharyngitis	-	-	-	4	2
Pharyngitis	-	✔	-	✔	-
Pharyngolaryngeal pain	-	-	-	✔	✔
Pharyngotonsillitis	-	-	-	✔	-
Pneumonia	-	-	-	✔	-
Rhinitis	-	-	-	✔	-
Seasonal allergies	-	-	-	✔	-
Sinus congestion	-	-	-	✔	-
Sinusitis	-	-	-	✔	-
Upper respiratory tract infection	-	-	-	3	-
Special Senses					
Abnormal visual accommodation	1	-	-	✔	-
Conjunctivitis	1	-	-	1	-
Diplopia	1	-	-	1	-
Eye pain	1	-	-	1	-
Ear pain	-	-	-	✔	-
Parosmia	1	-	-	✔	-
Taste perversion	-	-	-	✔	-
Tinnitus	1	-	-	✔	-
Visual disturbance	-	-	-	✔	-
Xerophthalmia	1	-	-	✔	-
Other					
Acute renal failure	-	-	✔	✔	-
Allergic reaction	1	-	✔	1	-
Angioedema	1	-	✔	✔	-
Contusion	-	-	-	✔	-
Epicondylitis	-	-	-	✔	-
Fatigue	4.5	✔	-	✔	2
Gingival hyperplasia	1	-	-	1	-
Hot flush	1	✔	-	✔	-
Hypersensitivity	-	-	-	✔	-
Lymphadenopathy	-	-	-	✔	-
Renal insufficiency	-	-	-	-	-
Rigors	1	-	-	1	-
Tooth abscess	-	-	-	✔	-
Toothache	-	-	-	✔	-
Tonsillitis	-	-	-	✔	-
Viral infection	-	-	-	✔	-
Weight gain	1	-	-	1	-
Weight loss	1	-	-	1	-

✔ Percent not specified
- Event not reported

Table 7. Adverse Drug Events (%) Reported with the Dihydropyridines (Drugs B - Z)[1,5-17]

Adverse Events	Felodipine	Isradipine	Nicardipine	Nifedipine	Nimodipine	Nisoldipine

Adverse Events	Felodipine	Isradipine	Nicardipine	Nifedipine	Nimodipine	Nisoldipine
Cardiovascular						
Angina (increased)	-	-	6	-	-	2
Arrhythmia	1 to 2	-	-	-	-	-
Atrial fibrillation	-	≤1	<1	-	-	-
Bradycardia	-	-	-	-	≤1	-
Cardiac failure	-	≤1	-	-	-	-
Cerebrovascular accident	-	-	-	-	-	1
Chest pain	1 to 2	-	-	-	-	-
Edema	-	4 to 36	≤1	-	≤1	-
Electrocardiogram abnormalities	-	-	≤1	-	≤1	-
Epistaxis	-	≤1	-	-	-	-
Erythromelalgia	-	-	-	1	-	-
Hypotension	1 to 2	≤1	- 5	5	1 to 50	-
Myocardial infarction	1 to 2	≤1	≤1	✔ ≤4	-	✔
Orthostatic hypotension	-	-	-	-	-	1
Palpitations	<3	1 to 5	3 to 4	<7	-	3
Pedal edema	-	-	6 to 8	-	-	-
Peripheral edema	2 to 17	4 to 40	6	7 to 29	-	22
Pericarditis	-	-	1	-	-	-
Peripheral ischemia	-	-	✔	-	-	-
Postural hypotension	-	-	≤1	-	-	-
Pulse irregularity	1 to 2	-	-	-	-	-
Rebound vasospasm	-	-	-	-	1	-
Tachycardia	1 to 2	1 to 3	1 to 4	-	≤1	-
Vasodilatation/vasodilation	-	-	1 to 5	-	-	4
Ventricular fibrillation	-	≤1	-	1	-	-
Ventricular tachycardia	-	-	≤1	-	-	-
Central Nervous System						
Anxiety	1 to 2	-	✔	-	-	-
Asthenia	2 to 4	1 to 6	-	<3	-	-
Ataxia	-	-	-	1	-	-
Balance difficulties	-	-	-	<2	-	-
Chills	-	-	-	<2	-	1
Confusion	-	-	✔	-	-	-
Depression	1 to 2	≤1	✔	1	≤1	-
Dizziness	3 to 4	3 to 8	1 to 7	4 to 27	-	5
Drowsiness	-	≤1	-	-	-	-
Fatigue	-	3 to 9	-	6	-	-
Headache	11 to 15	10 to 22	6 to 15	10 to 23	≤4	22
Insomnia	1 to 2	≤1	≤1	<3	-	-
Irritability	1 to 2	-	-	-	-	-
Migraine	-	-	-	1	-	1
Nervousness	1 to 2	≤1	≤1	<7	-	-
Numbness	-	≤1	-	-	-	-
Paresthesia	1 to 2	≤1	≤1	<3	-	-
Sleep disturbance	-	-	-	<2	-	-
Somnolence	1 to 2	-	≤1	<3	-	-
Stroke	-	≤1	-	-	-	-
Syncope	1 to 2	≤1	≤1	-	-	-
Transient ischemic attack	-	≤1	-	-	-	-
Tremor	-	-	≤1	<8	-	-
Vertigo	-	-	✔	1	-	-
Dermatologic						
Acne	-	-	-	-	≤1	-
Alopecia	-	-	-	<1	-	-
Dermatitis	-	-	-	1 to 2	-	-
Erythema	1 to 2	-	-	-	-	-
Flushing	4 to 7	1 to 5	6 to 10	3 to 25	-	✔
Hematoma	-	-	-	-	1	-
Hyperhidrosis	-	≤1	11	<2	-	-
Pruritus	-	≤1	-	<2	1	-
Rash	<2	≤3	≤1	<3	1 to 2	2
Urticaria	1 to 2	≤1	-	<2	-	-
Endocrine and Metabolic						
Breast pain	-	-	-	1	-	-
Decreased libido	1 to 2	-	-	-	-	-
Gout	-	-	-	1	-	-

Adverse Events	Felodipine	Isradipine	Nicardipine	Nifedipine	Nimodipine	Nisoldipine
Gynecomastia	1 to 2	-	-	-	-	-
Gastrointestinal						
Abdominal discomfort	-	≤5	-	<2	-	-
Abdominal pain	1 to 2	<1	-	<3	-	-
Acid regurgitation	1 to 2	-	-	-	-	-
Anorexia	-	-	-	-	-	1
Colitis	-	-	-	-	-	1
Constipation	<2	1 to 4	≤1	3	-	-
Diarrhea	1 to 2	≤3	-	<2	2 to 4	-
Dry mouth	1 to 2	≤1	≤1	<3	-	-
Dyspepsia	1 to 4	-	1 to 2	3 to 11	-	-
Dysphagia	-	-	-	-	-	1
Flatulence	1 to 2	-	-	<2	-	1
Gastritis	-	-	-	-	-	1
Gastrointestinal hemorrhage	-	-	-	-	1	1
Gastrointestinal symptoms	-	-	-	-	≤2	-
Hepatitis	-	-	-	-	1	1
Increased appetite	-	≤1	-	-	-	1
Jaundice	-	-	-	-	1	-
Nausea	1 to 2	1 to 5	2 to 5	3 to 11	≤1	2
Vomiting	1 to 2	≤1	≤5	-	-	-
Genitourinary						
Decreased libido	-	≤1	-	-	-	-
Dysuria	1 to 2	≤1	-	1	-	-
Hematuria	-	-	-	1	-	-
Impotence	1 to 2	≤1	✔	<3	-	-
Nocturia	-	≤1	-	1	-	-
Pollakiuria	-	1 to 3	-	-	-	-
Polyuria	1 to 2	-	-	1 to 3	-	-
Sexual dysfunction	-	-	-	<2	-	-
Urinary frequency/urgency	1 to 2	-	-	-	-	-
Hematological						
Anemia	1 to 2	-	-	<1	1	-
Leukopenia	-	≤1	-	-	-	-
Thrombocytopenia	-	-	✔	-	1	-
Laboratory Test Abnormalities						
Hepatic enzyme elevations	1 to 2	≤1	✔	-	≤1	-
Hyponatremia	-	-	-	-	1	-
Musculoskeletal						
Arthralgia	1 to 2	-	✔	<3	-	-
Back pain	1 to 2	≤1	-	1	-	-
Hypertonia	-	-	✔	1	-	-
Inflammation	-	-	-	<2	-	-
Joint sprain	1 to 2	≤1	-	-	-	-
Malaise	-	-	≤1	1	-	1
Muscle cramps	1 to 2	≤1	-	3 to 8	≤1	-
Muscle weakness	-	≤1	-	10 to 12	-	-
Musculoskeletal chest pain	1 to 2	2 to 3	-	<3	-	-
Myalgia	1 to 2	-	1	1	-	-
Neck pain	-	≤1	✔	-	-	-
Pain	-	-	≤1	<3	-	-
Stiffness	-	-	-	<2	-	-
Respiratory						
Bronchitis	1 to 2	-	-	-	-	-
Cough	1 to 2	≤1	-	1 to 6	-	-
Dyspnea	1 to 2	<3	≤1	3 to 6	≤1	-
Epistaxis	1 to 2	-	-	1	-	-
Influenza/flu-like illness	1 to 2	-	-	-	-	1
Nasal congestion	1 to 2	≤1	✔	2 to 6	-	-
Nasopharyngitis	1 to 2	-	-	-	-	-
Pharyngitis	-	-	-	-	-	5
Pharyngolaryngeal pain	-	≤1	-	-	-	-
Shortness of breath	-	≤1	-	<2	1	-
Sinusitis	1 to 2	-	✔	1	-	3
Sore throat	-	-	✔	6	-	-
Upper respiratory tract infection	1 to 4	-	-	1	-	-
Special Senses						

Adverse Events	Felodipine	Isradipine	Nicardipine	Nifedipine	Nimodipine	Nisoldipine
Abnormal visual accommodation	-	-	✔	1	-	-
Blurred vision	-	-	✔	<2	-	-
Conjunctivitis	-	-	✔	-	-	-
Ear pain/disorder	-	-	✔	-	-	-
Taste perversion	-	-	-	1	-	-
Tinnitus	-	-	✔	<5	-	-
Visual disturbance	1 to 2	≤1	-	<5	-	-
Other						
Allergic reaction	-	-	✔	-	-	-
Angioedema	1 to 2	-	-	-	-	-
Cellulitis	-	-	-	-	-	1
Contusion	1 to 2	-	-	-	-	-
Facial edema	-	-	-	-	-	1
Fever	-	≤1	-	<2	-	1
Gingival hyperplasia	1 to 2	-	-	-	-	1
Glossitis	-	-	-	-	-	1
Hot flush	-	-	✔	-	-	-
Infection	-	-	✔	-	-	-
Rigors	-	-	-	1	-	-
Warm sensation	1 to 2	-	-	-	-	-
Weight gain	-	≤1	-	1	-	-

✔ Percent not specified
- Event not reported

Table 8. Boxed Warning for Amlodipine and Benazepril[1]

WARNING
When pregnancy is detected, discontinue amlodipine and benazepril as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.

Table 9. Boxed Warning for Amlodipine and Olmesartan[1]

WARNING
When pregnancy is detected, discontinue amlodipine and olmesartan as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.

Table 10. Boxed Warning for Amlodipine and Valsartan[1]

WARNING
When pregnancy is detected, discontinue amlodipine and valsartan as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.

Table 11. Boxed Warning for Amlodipine and Valsartan and Hydrochlorothiazide[1]

WARNING
When pregnancy is detected, discontinue amlodipine and valsartan and hydrochlorothiazide as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.

Table 12. Boxed Warning for Nimodipine[1]

WARNING
Do not administer nimodipine intravenously or by other parenteral routes. Deaths and serious, life-threatening adverse reactions have occurred when the contents of nimodipine capsules have been injected parenterally.

VII. Dosing and Administration

The usual dosing regimens for the dihydropyridines are listed in Table 14.

Table 13. Usual Dosing Regimens for the Dihydropyridines[1,2,5-17]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Amlodipine	Angina pectoris (chronic stable and vasospastic): Solution, suspension, tablet: maintenance, 5 to 10 mg/day; maximum, 10 mg/day Coronary artery disease: Solution, suspension, tablet: maintenance, 5 to 10 mg/day; maximum, 10 mg/day Hypertension: Solution, suspension, tablet: initial, 2.5 to 5 mg/day maintenance, 5 to 10 mg/day; maximum, 10 mg/day	Hypertension in children six to 17 years of age: Solution, suspension, tablet: Initial, 2.5 mg/day; maintenance, 2.5 to 5 mg/day; maximum, 5 mg/day Safety and efficacy in children <6 years of age have not been established.	Solution: 1 mg/mL Suspension: 1 mg/mL Tablet: 2.5 mg 5 mg 10 mg
Felodipine	Hypertension: Extended-release tablet: initial, 5 mg/day; maintenance, 2.5 to 10 mg/day	Safety and efficacy in children have not been established.	Extended-release tablet: 2.5 mg 5 mg 10 mg
Isradipine	Hypertension: Capsule: initial, 2.5 mg twice daily; maximum, 20 mg/day	Safety and efficacy in children have not been established.	Capsule: 2.5 mg 5 mg
Levamlodipine	Hypertension: Tablet: initial, 1.25 to 2.5 mg once daily; maximum, 5 mg/day	Hypertension in children six to 17 years of age: Tablet: 1.25 to 2.5 mg once daily Safety and efficacy in children <6 years of age have not been established.	Tablet: 2.5 mg 5 mg
Nicardipine	Angina pectoris (chronic stable): Capsule: initial, 20 mg three times daily; maintenance, 20 to 40 mg three times daily Hypertension: Capsule: initial, 20 mg three times daily; maintenance, 20 to 40 mg three times daily Injection: titrate dose to achieve the desired blood pressure reduction; individualize dosage depending on the blood pressure to be obtained and the response of the patient	Safety and efficacy in children have not been established.	Capsule: 20 mg 30 mg Injection: 25 mg/10 mL
Nifedipine	Angina pectoris (chronic stable) Capsule: initial, 10 mg three times daily; maintenance, 10 to 20 mg three times daily; maximum, 180 mg/day	Safety and efficacy in children have not been established.	Capsule: 10 mg 20 mg Extended-release tablet: 30 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Extended-release tablet: initial, 30 or 60 mg/day; maintenance, 30 to 90 mg/day; maximum, 120 mg/day Angina pectoris (vasospastic): Capsule: initial, 10 mg three times daily; maintenance, 20 to 30 mg three to four times daily; maximum, 180 mg/day Extended-release tablet: initial, 30 or 60 mg/day; maintenance, 30 to 90 mg/day; maximum, 120 mg/day Hypertension: Extended-release tablet: initial, 30 or 60 mg/day; maintenance, 30 to 90 mg/day; maximum, 120 mg/day		60 mg 90 mg
Nimodipine	Subarachnoid hemorrhage: Capsule, solution: 60 mg every four hours for 21 consecutive days	Safety and efficacy in children have not been established.	Capsule: 30 mg Solution: 60 mg/20 mL
Nisoldipine	Hypertension: Extended-release tablet: initial, 20 mg once daily; maintenance, 20 to 40 mg/day; maximum, 60 mg/day Extended-release tablet (Sular® only): initial, 17 mg once daily; maintenance, 17 to 34 mg/day; maximum, 34 mg/day	Safety and efficacy in children have not been established.	Extended-release tablet: 8.5 mg 17 mg 20 mg 25.5 mg 30 mg 34 mg 40 mg
Combination Products			
Amlodipine and benazepril	Hypertension: Capsule: initial, 2.5-10 mg once daily; maintenance, individualize and adjust dosage according to clinical response, dose once daily	Safety and efficacy in children have not been established.	Capsule: 2.5-10 mg 5-10 mg 5-20 mg 5-40 mg 10-20 mg 10-40 mg
Amlodipine and olmesartan	Hypertension: Tablet: initial, 5-20 mg once daily; maximum, 10-40 mg once daily	Safety and efficacy in children have not been established.	Tablet: 5-20 mg 5-40 mg 10-20 mg 10-40 mg
Amlodipine and valsartan	Hypertension: Tablet: initial, 5-160 mg once daily; maximum, 10-320 mg once daily	Safety and efficacy in children have not been established.	Tablet: 5-160 mg 5-320 mg 10-160 mg 10-320 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Amlodipine and valsartan and HCTZ	Hypertension: Tablet: maximum, 10-320-25 mg once daily	Safety and efficacy in children have not been established.	Tablet: 5-160-12.5 mg 5-160-25 mg 10-160-12.5 mg 10-160-25 mg 10-320-25 mg

HCTZ=hydrochlorothiazide

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the dihydropyridines are summarized in Table 14.

Table 14. Comparative Clinical Trials with the Dihydropyridines

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Angina				
Koenig et al.[35] (1997) Amlodipine 5 to 10 mg QD for 4 weeks vs felodipine ER 5 to 10 mg QD for 4 weeks	DB, PRO, RCT, XO Patients, age 30 to 80 years, who have a history of angina, a positive exercise-stress test or positive 24-hour ambulatory monitoring, and ≥6 ischemic episodes in 24 hours	N=52 8 weeks	Primary: Number of ST-segment depressions in 24 hours of ambulatory monitoring Secondary: Total and mean duration of each ST-segment depression episode, maximum ST depression, length of ischemic episode, adverse events	Primary: Significant reductions from baseline were seen in both groups for the number of ST-segment depressions, from 19.9 at baseline for both groups to 2.3 for amlodipine and 2.4 for felodipine (P<0.001 for both from baseline; P=0.83 between treatments). Secondary: Total and mean duration of each ST-segment depression episode, maximum ST depression and length of ischemic episode were significantly different from baseline for both treatment groups, but treatments were not significantly different (P<0.001 for all from baseline, P=0.53, P=0.40, P=0.68, P=0.35, respectively between treatments). Adverse event rates similar between the treatments.
Savanitto et al.[36] (1996) <u>Weeks 1 to 6</u>: Nifedipine 20 mg BID vs metoprolol ER 200 mg QD <u>Weeks 7 to 10</u>:	DB, MC, RCT Patients with typical anginal symptoms that had been stable for approximately 6 months, who showed a positive response to exercise stress testing with 23 min of exercise tolerance and were in sinus	N=280 6 weeks	Primary: Angina frequency, exercise tolerance, safety Secondary: Not reported	Primary: At week six, both metoprolol (mean change, -1.95; 95 % CI, -1.25 to -2.64) and nifedipine (mean change, -1.57; 95 % CI, -0.69 to -2.45) significantly reduced the frequency of angina compared to baseline, but there was not a statistical difference between groups. At the end of 10 weeks, there was not a statistical difference observed between the groups. At week six, both metoprolol and nifedipine significantly increased the mean exercise time to l-mm ST-segment depression compared to baseline (both P<0.01); but metoprolol was significantly more effective than nifedipine (P<0.05). At week 10, the groups randomized to combination therapy had a further

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
nifedipine 20 mg BID plus placebo vs metoprolol ER 200 mg QD plus placebo vs metoprolol ER 200 mg QD and nifedipine 20 mg BID	rhythm and had an analyzable ST segment on ECG			increase in time to l-mm ST-segment depression (P<0.05 vs placebo). There were 14 cardiovascular events including one sudden death, three acute myocardial infarctions, eight cases of unstable angina, one of syncope and one of stroke and the incidence of these events did not differ among the treatment groups. Secondary: Not reported
Cardiovascular Outcomes Trials				
Pitt et al.[37] (2000) PREVENT Amlodipine 5 to 10 mg QD vs placebo	DB, MC, PC, RCT Men and women, age 30 to 80 years with angiographic evidence of CAD, DBP <95 mm Hg, TC 325 mg/dL, FBG <200 mg/dL	N=825 3 years	Primary: Change in mean minimal diameter with a quantitative coronary angiography Secondary: Progression of atherosclerosis in the carotid arteries assessed by B-mode ultrasonography for intimal-medial thicknesses, all-cause mortality, occurrence of major fatal/nonfatal vascular events or procedures, adverse events	Primary: Change, reduction, in the minimal diameter was similar between the amlodipine group and the placebo group (0.084 vs 0.0095 P=0.38). Secondary: Amlodipine treatment significantly decreased the progression of atherosclerosis as compared to placebo treatment, a 0.013 mm decrease for the amlodipine group vs a 0.033 mm increase with placebo (P=0.007). There was no difference in all-cause mortality between amlodipine and placebo. There was no difference in occurrence of fatal and nonfatal vascular events between the treatment groups (HR, 0.82; 95% CI, 0.47 to 1.42). Amlodipine treatment significantly reduced the occurrence of hospitalized CHF and unstable angina (HR, 0.65; 95% CI, 0.47 to 0.91) and coronary revascularizations (HR, 0.57; 95% CI, 0.41 to 0.81) and combined overall procedures (HR, 0.69; 95% CI, 0.52 to 0.92). There was no significant difference between groups in rates of adverse events: cancer rate (HR, 2.13; 95% CI, 0.90 to 5.21) and bleeding episode (HR, 1.42; 95% CI, 0.88 to 2.30).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dahlöf et al.[38] (2005) ASCOT-BPLA Amlodipine 5 to 10 mg/day adding perindopril 4 to 8 mg/day as needed vs atenolol 50 to 100 mg/day adding bendro-flumethiazide* 1.25 to 2.5 mg/day and potassium as needed If blood pressure was still not achieved, doxazosin 4 to 8 mg/day was added to the regimen.	MC, OL, RCT Patients 40 to 79 years of age with HTN and ≥3 other cardiovascular risk factors (left ventricular hypertrophy, other specified abnormalities on ECG, type 2 diabetes, PAD, history of stroke or TIA, male, age ≥55 years, microalbuminuria or proteinuria, smoking, TC:HDL-C ratio ≥6, or family history of CHD)	N=19,257 5.5 years	Primary: Nonfatal MI (including silent MI) and fatal CHD Secondary: All-cause mortality, total stroke, primary end points minus silent MI, all coronary events, total cardiovascular events and procedures, cardiovascular mortality, nonfatal and fatal heart failure, effects on primary end point and on total cardiovascular events and procedures among prespecified subgroups Tertiary: Silent MI, unstable angina, chronic stable angina, PAD, life-threatening arrhythmias, development of diabetes, development of	Primary: No statistically significant difference in nonfatal MI and fatal CHD was reported between the amlodipine plus perindopril group compared to the atenolol plus bendroflumethiazide groups (HR, 0.90; 95% CI, 0.79 to 12; P=0.1052). Secondary: Significantly greater reductions in the following secondary end points were observed with amlodipine plus perindopril compared to atenolol plus bendroflumethiazide: all- cause mortality (P=0.0247), total stroke (P=0.0003), primary end points minus silent MI (P=0.0458), all coronary events (P=0.0070), total cardiovascular events and procedures (P<0.0001), and cardiovascular mortality (P=0.0010). There were no significant differences in nonfatal and fatal heart failure between the two treatment groups (P=0.1257). The study was terminated early due to higher mortality and worse outcomes on several secondary end points observed in the atenolol study group. Tertiary: Significantly greater reductions in the following end points were observed with amlodipine plus perindopril compared to atenolol plus bendroflumethiazide: unstable angina (P=0.0115), PAD (P=0.0001), development of diabetes (P<0.0001), and development of renal impairment (P=0.0187). There were no significant differences in the incidence of silent MI (P=0.3089), chronic stable angina (P=0.8323) or life-threatening arrhythmias (P=0.8009) between the two treatment groups. There was no significant difference in the percent of patients who stopped therapy because of an adverse event between the two treatment groups (overall 25%). There was, however, a significant difference in favor of amlodipine plus perindopril in the proportion of patients who stopped trial therapy because of a serious adverse events (2 vs 3%; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			renal impairment	
Chapman et al.[39] (2007) ASCOT-BPLA Atenolol 50 to 100 mg titrated to target blood pressure <140/90 mm Hg (or <130/90 mm Hg in diabetic patients); bendro-flumethiazide* plus potassium 1.25 to 2.5 mg plus doxazosin were added for additional blood pressure control; if blood pressure remained elevated on the 3 above drugs, spironolactone 25 mg was added to the regimen vs amlodipine 5 to 10 mg titrated to target blood pressure <140/90 mm Hg (or <130/90 mm Hg in diabetic patients); perindopril 4 to 8 mg and doxazosin were added for	Sub analysis of ASCOT-BPLA evaluating effects of spironolactone on treatment-resistant HTN Patients 40 to 79 years of age with HTN and ≥3 cardiovascular risk factors, with SBP ≥160 mm Hg and/or DBP ≥100 mm Hg (not on antihypertensive therapy) or SBP ≥140 mm Hg and/or DBP ≥90 mm Hg (on antihypertensive therapy)	N=1,411 1.3 years	Primary: Change in DBP and SBP, adverse effects Secondary: Not reported	Primary: Spironolactone-treated patients lead to a significant 21.9 mm Hg reduction in SBP among patients whose blood pressure was previously uncontrolled on at least three other antihypertensive drugs (95% CI, 20.8 to 23.0 mm Hg; P<0.001). Spironolactone-treated patients lead to a significant 9.5 mm Hg reduction in DBP among patients whose blood pressure was previously uncontrolled on at least three other antihypertensive drugs (95% CI, 9.0 to 10.1; P<0.001). Spironolactone-treated patients exhibited small but significant decreases in sodium, LDL-C and TC as well as increases in potassium, glucose, creatinine and HDL-C (P<0.05). The most common adverse effect reported in the trial was gynecomastia in men (P value not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
additional control; if blood pressure remained elevated on the 3 above drugs, spironolactone 25 mg was added to the regimen				
Nissen et al.[40] (2004) CAMELOT Amlodipine 10 mg/day vs enalapril 20 mg/day vs placebo	DB, MC, PC, RCT Patients 30 to 79 years of age requiring coronary angiography for evaluation for chest pain or PCI and a diastolic pressure <100 mm Hg, with or without treatment	N=1,991 2 years	Primary: Composite of cardiovascular events (cardiovascular death, nonfatal MI, resuscitated cardiac arrest, coronary revascularization, hospitalization for angina pectoris, hospitalization for CHF, fatal or nonfatal stroke or TIA, and any new diagnosis of PVD), nominal change in percent atheroma volume (substudy) Secondary: Incidence of adverse events; all-cause mortality, incidence of revascularization in vessels that had undergone	Primary: Cardiovascular events occurred in 23.1% of placebo-treated patients, 16.6% amlodipine-treated patients (HR, 0.69; 95% CI, 0.54 to 0.88; P=0.003) and 20.2% enalapril-treated patients (HR, 0.85; 95% CI, 0.67 to 17; P=0.16). The primary end point comparison for enalapril vs amlodipine was not significant (HR, 0.81; 95% CI, 0.63 to 14; P=0.10). Secondary: Coronary revascularization was reduced in the amlodipine group from 15.7 to 11.8% (HR, 0.73; 95% CI, 0.54 to 0.98; P=0.03). Hospitalization for angina was reduced in the amlodipine group from 12.8 to 7.7% (HR, 0.58; 95% CI, 0.41 to 0.82; P=0.002). Individual components of the primary end point generally showed fewer events with enalapril treatment vs placebo, but none of the comparisons reached statistical significance. For components of the primary end point, only the rate of hospitalization for angina showed a statistically significant difference between amlodipine and enalapril (HR, 0.59; 95% CI, 0.42 to 0.84; P=0.003). A trend toward fewer episodes of revascularization in patients undergoing intervention at baseline was observed for amlodipine vs enalapril (HR, 0.66; 95% CI, 0.40 to 16; P=0.09). The mean change in percent atheroma volume was 0.5% for amlodipine (P=0.12 vs placebo), 0.8% for enalapril (P=0.32 vs placebo) and 1.3% for placebo. In patients with SBP greater than the mean, the amlodipine group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			previous stent placement	showed a significantly slower progression (0.2%) compared to placebo (2.3%; P=0.02). Compared to baseline, intravascular ultrasound showed progression in patients receiving placebo (P<0.001), a trend toward progression with enalapril (P=0.08) and no progression in patients receiving amlodipine (P=0.31). For the amlodipine group, correlation between blood pressure reduction and progression was r=0.19 (P=0.07). Discontinuation from the study for treatment-emergent adverse events was low, averaging 0.4% and not statistically significant between the three treatment groups. The only statistically significant difference in secondary end points was that amlodipine demonstrated a significant reduction in revascularization after previous stent placement compared to placebo (4.1 vs 7.9%; HR, 0.49; 95% CI, 0.31 to 0.78; P=0.002). The rate of revascularization was lower than enalapril (6.2%) but not statistically significant (HR, 0.66; 95% CI, 0.40 to 16; P=0.09).
ALLHAT[41] (2002) ALLHAT Amlodipine 2.5 to 10 mg/day vs lisinopril 10 to 40 mg/day vs chlorthalidone 12.5 to 25 mg/day	DB, MC, RCT Patients ≥55 years with HTN and ≥1 additional CHD risk factor	N=33,357 4.9 years (mean)	Primary: Combined fatal CHD or nonfatal MI Secondary: All-cause mortality, fatal and nonfatal stroke, combined CHD, combined cardiovascular disease (combined CHD, stroke, treated angina without hospitalization, heart failure, and PAD)	Primary: There were no significant differences in the primary outcome between lisinopril (11.4%), amlodipine (11.3%), and chlorthalidone (11.5%). Secondary: All-cause mortality did not differ between groups. Five year SBPs were significantly higher in the lisinopril (2 mm Hg; P<0.001) and amlodipine groups (0.8 mm Hg; P=0.03) compared to chlorthalidone, and five year DBPs were significantly lower with amlodipine (0.8 mm Hg; P<0.001). Amlodipine had a higher six year rate of heart failure compared to chlorthalidone (10.2 vs 7.7%; RR, 1.38; 95% CI, 1.25 to 1.52). Lisinopril had a higher six year rate of combined cardiovascular disease (33.3 vs 30.9%; RR, 1.10; 95% CI, 15 to 1.16); stroke (6.3 vs 5.6%; RR, 1.15; 95% CI, 12 to 1.30) and heart failure (8.7 vs 7.7%; RR, 1.19; 95% CI, 17 to 1.31).
Black et al.[42]	MC, RCT	N=17,515	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2008) ALLHAT Amlodipine 2.5 to 10 mg QD vs lisinopril 10 to 40 mg QD vs chlorthalidone 12.5 to 25 mg QD	Men and women, age 55 years old and older, with HTN and metabolic syndrome	4.9 years (mean)	Fatal coronary heart disease and nonfatal MI Secondary: All cause mortality, fatal and nonfatal stroke, combined coronary heart disease, combined cardiovascular disease	For patients with metabolic syndrome, there was no significant difference in rates of coronary heart disease and nonfatal MI with amlodipine vs chlorthalidone (RR, 0.96; 95% CI, 0.79 to 1.16), or lisinopril vs chlorthalidone (RR, 15; 95% CI, 0.88 to 1.27). Secondary: For patients with metabolic syndrome, there were no significant differences found between amlodipine vs chlorthalidone in all secondary endpoints (P value not significant). For patients without metabolic syndrome, amlodipine treatment was associated with significantly more heart failure, but in patients with metabolic syndrome, there was no difference (P=0.03). Patients with metabolic syndrome who received lisinopril experienced more heart failure and cardiovascular disease than those who received chlorthalidone (RR, 1.31; 95% CI, 14 to 1.64 and RR, 1.19; 95% CI, 17 to 1.32).
Rahman et al.[43] (2012) ALLHAT Amlodipine 2.5 to 10 mg/day vs lisinopril 10 to 40 mg/day vs chlorthalidone 12.5 to 25 mg/day	Long-term, post-trial, follow-up Patients in ALLHAT stratified based on eGFR	N=31,350 4 to 8 years	Primary: Cardiovascular mortality Secondary: Total mortality, CHD, cardiovascular disease, stroke, heart failure, ESRD	Primary: After an average of 8.8 years of follow-up, total mortality was significantly higher in patients with moderate/severe eGFR reduction (eGFR <60 mL/min/1.73 m^2) compared to patients with normal/increased (eGFR ≥90 mL/min/1.73 m^2) and mildly reduced eGFR (eGFR 60 to 89 mL/min/1.73 m^2) (P<0.001). In patients with moderate/severe eGFR reduction, there was no significant difference in cardiovascular mortality between chlorthalidone and amlodipine (P=0.64), or chlorthalidone and lisinopril (P=0.56). Secondary: No significant differences were observed for any of the secondary endpoints among eGFR reduction groups.
Muntner et al.[44] (2014) ALLHAT	Post-hoc analysis of ALLHAT	N=24,004 6 to 28 months	Primary: Visit-to-visit variability (VVV)	Primary: Each measure of VVV of SBP was lower among participants randomized to chlorthalidone and amlodipine compared with those randomized to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Chlorthalidone 12.5 to 25 mg/day vs amlodipine 2.5 to 10 mg/day vs lisinopril 10 to 40 mg/day	Patients in ALLHAT with 5, 6, or 7 visits in 6 to 28 months of follow-up		of blood pressure Secondary: Not reported	lisinopril. All four VVV of SBP metrics were lower among participants randomized to amlodipine vs chlorthalidone after full multivariable adjustment. After multivariable adjustment including mean SBP across visits and compared with participants randomized to chlorthalidone, participants randomized to amlodipine had a 0.36 (standard error [SE]: 0.07) lower standard deviation (SD) of SBP and participants randomized to lisinopril had a 0.77 (SE=0.08) higher SD of SBP. Results were consistent using other VVV of SBP metrics. These data suggest chlorthalidone and amlodipine are associated with lower VVV of SBP than lisinopril. Secondary: Not reported
Bangalore et al.[45] (2017) ALLHAT Amlodipine 2.5 to 10 mg/day vs lisinopril 10 to 40 mg/day vs chlorthalidone 12.5 to 25 mg/day	Post-hoc analysis of ALLHAT Patients in ALLHAT with average blood pressure ≥140 mmHg systolic or ≥90 mm Hg diastolic on ≥3 antihypertensive medications, or blood pressure <140/90 mmHg on ≥4 antihypertensive medications (i.e., identified as having apparent treatment-resistant hypertension) at 2-year follow up	N=14,684 4.9 years (mean)	Primary: Combined fatal CHD or nonfatal MI Secondary: All-cause mortality, fatal and nonfatal stroke, combined CHD, combined cardiovascular disease (combined CHD, stroke, treated angina without hospitalization, heart failure, and PAD)	Primary: Of participants assigned to chlorthalidone, amlodipine, or lisinopril, 9.6%, 11.4%, and 19.7%, respectively, had treatment-resistant hypertension. During mean follow-up of 2.9 years, primary outcome incidence was similar for those assigned to chlorthalidone compared with amlodipine or lisinopril (amlodipine- vs chlorthalidone-adjusted HR, 0.86; 95% CI, 0.53 to 1.39; P=0.53; lisinopril- vs chlorthalidone-adjusted HR, 1.06; 95% CI, 0.70 to 1.60; P=0.78). Secondary: Secondary outcome risks were similar for most comparisons except coronary revascularization, which was higher with amlodipine than with chlorthalidone (HR, 1.86; 95% CI, 1.11 to 3.11; P=0.02). An as-treated analysis based on diuretic use produced similar results.
Ogihara et al.[46] (2008)	AC, MC, OL, RCT	N=4,703	Primary: First fatal or	Primary: A total of 134 patients experienced a cardiovascular event in each

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
CASE-J Amlodipine 2.5 to 10 mg QD vs candesartan 4 to 12 mg QD	Patients with high risk HTN (SBP ≥140 mm Hg or DBP ≥90 mm Hg in patients <70 years old or SBP ≥160 mm Hg or DBP ≥90 mm Hg in patients ≥70 years old), with either type 2 diabetes, history of stroke or ischemic attack, left ventricular hypertrophy, proteinuria or serum creatinine ≥1.3 mg/dL	Up to 4 years	nonfatal cardiovascular event Secondary: All-cause death, new-onset diabetes, discontinuation due to adverse events	treatment regimen (HR, 10; 95% CI, 0.78 to 1.27; P=0.969). Secondary: All-cause death rates did not differ between treatments, 73 deaths in the candesartan group and 86 in the amlodipine group. New-onset diabetes occurred in significantly fewer patients in the candesartan group than the amlodipine group (HR, 0.64; 95% CI, 0.43 to 0.97; P=0.033). A total of 125 (5.4%) patients in the candesartan group and 134 (5.8%) of patients in the amlodipine group discontinued due to adverse events.
Julius et al.[47] (2004) VALUE Amlodipine 5 to 10 mg QD vs valsartan 80 to 160 mg QD	DB, PG, RCT Patients ≥50 years old with treated or untreated HTN and history of cardiovascular disease, stroke, or diabetes, previous medications were discontinued at trial onset	N=15,245 4.2 years (mean)	Primary: Time to first cardiac event (cardiac morbidity and mortality) Secondary: Fatal and nonfatal MI, fatal and nonfatal heart failure and fatal and nonfatal stroke, all-cause mortality, new onset diabetes	Primary: There were no differences in the primary composite end point between the valsartan and amlodipine groups (10.6 vs 10.4%; P=0.49). Secondary: There was a higher incidence of myocardial infarction (4.8 vs 4.1%; P=0.02) in patients receiving valsartan than amlodipine. There was no difference in the incidence of heart failure (4.6 vs 5.3%; P=0.12), stroke (4.2 vs 3.7%; P=0.08), and all-cause mortality (11 vs 10.8%; P=0.45) between valsartan- and amlodipine-treated patients. New onset diabetes occurred less with valsartan (13.1%) vs amlodipine (16.4%; P<0.001). Combined target blood pressure (<140/90 mm Hg) was achieved in 58% and 62% of patients receiving valsartan and amlodipine, respectively.
Zanchetti et al.[48] (2006)	Subgroup analysis of VALUE	N=15,245	Primary: Time to first	Primary: The only significant result of the analyses by subgroup for time to first

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
VALUE Amlodipine 5 mg QD vs valsartan 80 mg QD	Patients with HTN	4.2 years	cardiac event, analyzed by subgroup Secondary: MI, heart failure and stroke	cardiac event was sex; women in the valsartan group experienced more cardiac events as compared to men in the valsartan group (HR for women, 1.21; 95% CI, 13 to 1.42; HR for men, 0.94; 95% CI, 0.82 to 17; P=0.016). The VALUE trial showed no difference in the primary outcome as well as in cardiac morbidity and mortality between amlodipine treatment and valsartan treatment. SBP and DBP were lower, as was incidence of MI, in the amlodipine treatment group as compared to the valsartan group. Secondary: Male patients treated with valsartan had a significantly lower incidence of heart failure than males treated with amlodipine (P<0.001 for male vs female difference; for men, HF rates with valsartan were 4.1% vs amlodipine 5.8% [HR, 0.73; 95% CI, 0.60 to 0.88]; for women, rates were valsartan 5.3% vs amlodipine 4.6%, [HR, 1.18; 95% CI, 0.95 to 1.47]). Patients without a history of stroke had a greater reduction in stroke risk if treated with amlodipine (valsartan 3.4% vs amlodipine 2.6%; HR, 1.34; 95% CI, 19 to 1.65).
Jamerson et al.[49] (2008) ACCOMPLISH Amlodipine 5 mg QD and benazepril 20 mg QD vs benazepril 20 mg QD and HCTZ 12.5 mg QD	AC, DB, MC, RCT Patients >60 years of age with HTN and at high risk of cardiovascular events	N=11,506 36 months (mean)	Primary: The composite of death from cardiovascular causes, nonfatal MI, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and coronary revascularization. Secondary: Death from	Primary: There were 552 primary-outcome events in the benazepril plus amlodipine group (9.6%) and 679 events in the benazepril plus HCTZ group (11.8%). The absolute risk reduction with benazepril plus amlodipine therapy was 2.2% and the relative risk reduction was 19.6% compared to benazepril plus HCTZ (HR, 0.80; 95% CI, 0.72 to 0.90; P<0.001). Secondary: For the secondary end point of death from cardiovascular causes, nonfatal MI, and nonfatal stroke, there were 288 (5%) events in the benazepril plus amlodipine group compared to 364 (6.3%) events in the benazepril plus HCTZ group. The absolute risk reduction with benazepril plus amlodipine therapy was 1.3% and the RR reduction was 21.2% compared to benazepril plus HCTZ (HR, 0.79; 95% CI, 0.67 to 0.92; P=0.002).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			cardiovascular causes, nonfatal MI, and nonfatal stroke	
Bakris et al.[50] (2010) ACCOMPLISH Benazepril and amlodipine 40-5 to 40-10 mg/day, followed by forced titration after 1 month on benazepril and amlodipine 20-5 mg (fixed-dose combination product) vs benazepril and HCTZ 40-12.5 to 40-25 mg/day, followed by forced titration after 1 month on benazepril and HCTZ 20-12.5 mg (fixed-dose combination product)	Prespecified sub analysis of ACCOMPISH Men and women >60 years of age with HTN and at high risk for cardiovascular events (history of coronary events, MI, revascularization, or stroke; impaired renal function; PAD, left ventricular hypertrophy; or diabetes)	N=11,482 2.9 years (mean duration)	Primary: Time to first event of doubling of serum creatinine concentration or end stage renal disease (defined as eGFR <15 mL/min/1.73 m^2 or need for chronic dialysis) Secondary: Progression of chronic kidney disease plus death, change in albuminuria, and change in eGFR	Primary: There were fewer chronic kidney disease events in the benazepril and amlodipine group (2.0% of patients) compared to the benazepril and HCTZ group (3.7%; HR, 0.52; 95% CI, 0.41 to 0.65; P<0.0001). Secondary: The composite endpoint of progression of chronic kidney disease and all-cause mortality was lower in the benazepril and amlodipine group (6.0%) compared to the benazepril and HCTZ group (8.1%; HR, 0.73; 95% CI, 0.64 to 0.84; P<0.0001). There was a slower decline in eGFR in the benazepril and amlodipine group compared to the benazepril and HCTZ group (-0.88 vs -4.22 mL/min/1.73 m^2; P=0.01). Of the patients with baseline microalbuminuria, there was a reduction in the urinary albumin:creatinine in the benazepril and HCTZ group of -63.8% (median change) compared to a median change of -29.0% in the benazepril and amlodipine group (P<0.0001). There was a higher percentage of patients reporting peripheral edema in the benazepril and amlodipine group compared to the benazepril and HCTZ group (P<0.0001).
Weber et al.[51] (2010) ACCOMPLISH Benazepril and amlodipine 40-5 to	Prespecified subanalysis of ACCOMPISH Men and women >60 years of age	N=6,946 Mean treatment duration 29.7 months for	Primary: Primary: Time to first event (composite of cardiovascular event and death	Primary: The primary endpoint occurred in 8.8% of diabetic patients in the benazepril and amlodipine group and 11.0% in the benazepril and HCTZ group (HR, 0.79; P=0.003; NNT, 46). In high risk diabetic patients, 13.6% of patients in the benazepril and amlodipine group and 17.3% in the benazepril and HCTZ group (HR, 0.77, P=0.007; NNT, 28).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
40-10 mg/day, followed by forced titration after 1 month on benazepril and amlodipine 20-5 mg (fixed-dose combination product) vs benazepril and HCTZ 40-12.5 to 40-25 mg/day, followed by forced titration after one month on benazepril and HCTZ 20-12.5 mg (fixed-dose combination product)	with HTN and at high risk for cardiovascular events (history of coronary events, MI, revascularization, or stroke; impaired renal function; peripheral arterial disease, left ventricular hypertrophy; or diabetes) (Subanalysis of patients with diabetes)	benazepril and amlodipine group and 29.5 months for benazepril and HCTZ group	from cardiovascular causes) Secondary: Composite of cardiovascular events (the primary endpoint excluding fatal events) and composite of death from cardiovascular disease, nonfatal stroke and nonfatal MI	Secondary: Due to early termination, the study had limited power to detect differences in the diabetic subgroups. Peripheral edema was higher in the benazepril and amlodipine group compared to the benazepril and HCTZ group.
Weber et al.[52] (2013) ACCOMPLISH Benazepril and amlodipine 40-5 to 40-10 mg/day, followed by forced titration after 1 month on benazepril and amlodipine 20-5 mg (fixed-dose combination product) vs	Subanalysis of ACCOMPLISH based on body size Patients >60 years of age with HTN and at high risk of cardiovascular events	N=11,482	Primary: Composite of cardiovascular death or nonfatal MI or stroke Secondary: Cardiovascular death, total MI, total stroke	Primary: In patients receiving benazepril and HCTZ, the primary endpoint (per 1,000 patient-years) was 30.7 in normal weight (BMI <25), 21.9 in overweight (BMI ≥25 to <30), and 18.2 in obese patients (BMI ≥30) (overall P=0.0034). In patients receiving benazepril and amlodipine, the primary endpoint did not differ between the three BMI groups (18.2, 16.9, and 16.5, respectively; P=0.9721). In obese patients, primary event rates were similar between the two treatments, but rates were significantly lower with benazepril and amlodipine in overweight patients (HR, 0.76; 95% CI, 0.59 to 0.94; P=0.0369) and normal weight patients (HR, 0.57; 95% CI, 0.39 to 0.84; P=0.0037). Secondary: Comparing obese and overweight patients, event rates were all numerically lower, but not significantly lower, in obese patients. Cardiovascular deaths were significantly lower in overweight patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
benazepril and HCTZ 40-12.5 to 40-25 mg/day, followed by forced titration after 1 month on benazepril and HCTZ 20-12.5 mg (fixed-dose combination product)				compared to normal weight patients (HR, 57; 95% CI, 0.37 to 0.89; P=0.0125). Cardiovascular death (HR, 0.40; 95% CI, 0.25 to 0.63; P<0.0001) and total stroke (HR, 0.60; 95% CI, 0.37 to 0.96; P=0.0335) were significantly lower in obese patients compared to normal weight patients.
Bakris et al.[53] (2013) ACCOMPLISH HCTZ 12.5 to 25 mg QD and benazepril 20 to 40 mg QD (B+H) vs benazepril 20 to 40 mg QD and amlodipine 5 to 10 mg QD (B+A)	Post hoc analysis Patients included in the ACCOMPLISH trial (>60 years of age with HTN and at high risk of cardiovascular events) stratified by presence of known CAD at baseline	N=11,506 36 months (mean)	Primary: The composite of death from cardiovascular causes, nonfatal MI, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and coronary revascularization. Secondary: Death from cardiovascular causes, nonfatal MI, and nonfatal stroke	Primary: Among the patients with CAD, 13% in the B+A group and 16% in the B+H group reached the primary end point, representing an absolute risk reduction of 3% and a hazard reduction of 18%. The difference in event rates of the composite primary end point between the B+A and B+H groups was significant (HR, 0.80; 95% CI, 0.69 to 0.92; P=0.0016). Among the patients without CAD, fewer patients in the B+A treatment arm (204 of 3,096) reached the primary end point compared with those in the B+H arm (251 of 3,095). The difference in event rates between the B+A and B+H groups was significant (HR, 0.81; 95% CI, 0.67 to 0.98; P=0.026). A comparison of patients with and without CAD event rates for the primary end points demonstrated that the patients with CAD had a greater CV event rate than those without CAD (15 vs 7%; P<0.0001). Secondary: The composite secondary end point of CV mortality, MI, and stroke occurred in 5.74% in the B+A group and 8% in the B+H group, resulting in an absolute risk reduction of 1.95% and a hazard reduction of 25% (HR, 0.73; 95% CI, 0.59 to 0.9; P=0.033). The rate of all-cause mortality differed significantly between the treatment arms (HR, 0.77; 95% CI, 0.6 to 0.99; P=0.042). Among the patients without CAD, the rates of CV mortality, MI, and stroke did not differ between the two arms (HR, 0.86; 95% CI, 0.68 to 1.08). The secondary end point events were lower in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				group of patients without CAD.
Hansson et al.[54] (1999) STOP-Hypertension Felodipine 2.5 mg or isradipine 2.5 mg QD vs enalapril 10 mg or lisinopril 10 mg QD vs atenolol 50 mg or metoprolol 100 mg or pindolol 5 mg QD and/or HCTZ 25 mg with amiloride 2 to 5 mg QD	MC, OL, PRO, RCT Men and women, age 70to 84 years with HTN (SBP ≥180mm Hg or DBP ≥105 mm Hg or both)	N=6,614 4 years	Primary: Fatal stroke, fatal MI, other fatal cardiovascular events Secondary: Blood pressure	Primary: The rate of prevention of cardiovascular deaths was similar in all groups (RR, 0.97 to 14; 95% CI, 0.86 to 1.26). Fatal cardiovascular events, including fatal stroke and fatal myocardial infarction MI, occurred in 19.8 per 1,000 patient-years in the β-blocker and/or HCTZ group, in the felodipine or isradipine group and in the enalapril or lisinopril group (RR, 0.99; 95% CI, 0.84 to 1.16). The RR of cardiovascular death in patients in the enalapril or lisinopril group as compared to the felodipine or isradipine group was 14 (95% CI, 0.86 to 1.26; P=0.67.) Secondary: Decreases in blood pressure were similar among the groups.
Borhani et al.[55] (1996) MIDAS Isradipine 2.5 to 5 mg BID vs HCTZ 12.5 to 25 mg QD	DB, MC, positive-control, RCT Patients, average of 58.5 years old, with HTN	N=883 3 years	Primary: Rate of progression of intimal-medial thickness in carotid arteries Secondary: Rate of cardiovascular events (MI, stroke, CHF, angina, sudden death), rate of non-major cardiovascular events and	Primary: There was no difference in the rate of progression of intimal-medial thickness between the treatment groups (P=0.68). Secondary: The rate of cardiovascular events was greater in the isradipine group than in the HCTZ group (5.65 vs 3.17%; P=0.07). The rate of non-major cardiovascular events was greater in the isradipine group than in the HCTZ group (9.05 vs 5.22%; P=0.02). There was a significant decrease in SBP in the HCTZ group as compared to isradipine (-19.5 vs -16.0 mm Hg; P=0.002). There was no difference in change in DBP (both groups, -13.0 mm Hg).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			procedures (TIAs, dysrhythmia, aortic valve replacement, femoral popliteal bypass graft), blood pressure	
National Intervention Cooperative Study[56] (1999) NICS-EH Nicardipine SR 20 mg BID vs trichlor-methiazide* 2 mg QD	DB, RCT Patients age 60 years old and older with a SBP between 160 to 220 mm Hg and a DBP <115 mm Hg and no history of cardiovascular complications	N=414 5 years	Primary: Cardiovascular complications Secondary: Blood pressure, pulse, side effects, laboratory values	Primary: There was no difference in rate of cardiovascular complications during the study period (P=0.923). There was no difference in the number of patients experiences left ventricular hypertrophy on ECG (P=0.975). Secondary: Both groups experienced significant reductions in blood pressure from baseline (P=0.000). There was no significant difference in pulse rate between the groups. Side-effect rates did not differ between the groups (P=0.897). More patients in the trichlormethiazide group than in the nicardipine group had abnormal lab results at the end of the study; differences were significant for serum sodium levels (decreased in the trichlormethiazide group) and uric acid levels (increased with trichlormethiazide).
Lichtlen et al.[57] (1990) INTACT Nifedipine 80 mg QD vs placebo	DB, MC, PC, RCT Patients, age 65 years and younger, demonstrating early CAD who were not candidates for invasive therapeutic procedures	N=348 3 years	Primary: Progression of coronary artery disease detected on angiogram (change in minimal diameter, percent stenosis, transition into occlusion, new stenosis) Secondary:	Primary: In patients without study deviations, there were no significant differences in number of stenoses and occlusions per patient (nifedipine=3.7, placebo=3.88; P=0.437). The distribution among the arteries of the occlusions was not different between groups. The progression of stenosis was significant from baseline but changes were not significantly different between the groups (P<0.006 for all vs baseline; P>0.585 for group comparisons). Secondary: There was no difference between nifedipine treatment and placebo in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Critical clinical events (cardiac death, nonfatal MI, unstable angina, need for procedure, heart failure, severe arrhythmias), progression of new lesions	number of critical events, 44 events in 24 patients receiving nifedipine vs 52 events in 35 patients in the placebo group (P=0.278). The nifedipine group had significantly fewer new lesions as compared to the placebo group: 78 (0.58 lesions/patients) vs 118 (0.8 lesions/patient) (P=0.031).
Brown et al.[58] (2000) INSIGHT Nifedipine 30 mg QD vs amiloride and HCTZ 2.5-25 mg QD (fixed-dose combination product) Doses were doubled or atenolol 25 to 50 mg or enalapril 5 to 10 mg was added.	DB, MC, PRO, RCT Patients, age 55 to 80 years old with HTN (blood pressure ≥150/95 mm Hg or SBP ≥160 mm Hg) and ≥1 cardiovascular risk factor	N=6,575 3 years	Primary: Composite death from any cardiovascular cause together with nonfatal stroke, MI, or heart failure Secondary: Total mortality, death from a vascular cause, nonfatal vascular event	Primary: There was no difference in composite cardiovascular deaths between the groups. Events occurred in 200 (6.3%) patients in the nifedipine group and 182 (5.8%) of the amiloride and HCTZ group (18.2 vs 16.5 events per 1,000 patient-years; P=0.34). Secondary: There was no difference in all-cause mortality (P=0.62), death from a vascular cause (P=0.67) and in nonfatal vascular events (P=0.50) between the treatment groups.
Estacio et al.[59] (1998) ABCD Nisoldipine 10 to 60 mg/day vs	DB, PRO, RCT Patients between the ages of 40 and 74 years with NIDDM, baseline DBP ≥90 mm Hg and receiving no	N=470 67 months	Primary: Effect of intensive (target DBP of 75 mm Hg) or moderate (target DBP between 80 to 89 mm Hg) blood pressure control on	Primary: Analysis of the 470 patients in the trial who had HTN (DBP ≥90 mm Hg) showed similar control of blood pressure, blood glucose and lipid concentrations between the two study medications throughout the five years of follow-up. Secondary: Nisoldipine was associated with a higher incidence of fatal and nonfatal

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
enalapril 5 to 40 mg/day	antihypertensive medications at the time of randomization		the incidence and progression of complications of diabetes; compare enalapril to nisoldipine as a first-line antihypertensive agent Secondary: Incidence of MI	MI than enalapril (RR, 7.0; 95% CI, 2.3 to 21.4).
Hypertension				
Sheehy et al.[60] (2000) Amlodipine 2.5 to 10 mg QD vs felodipine 2.5 to 10 mg QD	RETRO Patients, age 65 years and older, with HTN	N=7,818 Duration not reported	Primary: Prescription renewal, drug switch rates, compliance rates, office visits Secondary: Not reported	Primary: Patients prescribed amlodipine had a greater compliance rate, 67.9%, than those prescribed felodipine 66.2% (P<0.01). Discontinuation rates were higher in the felodipine group by 27%. Amlodipine treatment resulted in more continuous months of treatment (69.2), than felodipine treatment (57.8) (P<0.01). Renewal rates were significantly larger in the amlodipine group (89.0%), than the felodipine group (85.6%) (P<0.01). Switch rates were significantly larger, 5 times, in the felodipine group (10.2%) than the amlodipine group (1.9%) (P<0.01). Visits to specialists occurred significantly more in patients treated with amlodipine than felodipine, (OR, 1.14; 95% CI, 18 to 1.20). Secondary: Not reported
Van der Krogt et al.[61] (1996)	DB, MC, PG, RCT Patients, age 18 to 75 years old, with	N=201 12 weeks	Primary: Number of responders (DBP ≤90 mm Hg after	Primary: Amlodipine treatment resulted in significantly more responders than felodipine treatment (P=0.046): 68% (69 of 101) of the amlodipine group were responders.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Amlodipine 5 to 10 mg QD vs felodipine ER 5 to 10 mg QD	mild to moderate HTN (DBP ≥95 mm Hg and ≤114 mm Hg)		12 weeks of monotherapy or decrease of >10 mm Hg if baseline DBP >100 mm Hg) who did not experience serious adverse events Secondary: Blood pressure, adverse events	53% (49 of 92) of the felodipine group were responders. 32% (32 of 101) of the amlodipine group were not responders. 47% (43 of 92) of the felodipine group were not responders. Secondary: The decreases in SBP and DBP from baseline were significant within each group, but were similar between the groups (amlodipine SBP and DBP 12 weeks vs baseline; P<0.001, felodipine SBP and DBP 12 weeks vs baseline; P<0.001, amlodipine 12 week change vs felodipine 12 week change; P>0.05). Adverse events were experienced by 33% of the amlodipine group and 42% of the felodipine group. Significantly more patients in the felodipine group experienced serious adverse events (9 patients who experienced 17 serious events vs two patients who experienced three serious events; P=0.048).
Mounier-Vehier et al.[62] (2002) Amlodipine 5 mg QD vs nicardipine 60 mg/day, divided 2 to 3 times daily	DB, MC, PG RCT Men and women, age 60 years and older with isolated systolic HTN (SBP 160 to 208 mm Hg) and DBP <90 mm Hg	N=133 90 days	Primary: Mean difference in SBP from baseline to day 90 Secondary: Mean difference in DBP, pulse pressure, heart rate, percent of patients with normal blood pressure (<140/90 mm Hg), safety	Primary: The decrease in SBP from baseline was significant within each group, but were similar between the groups (amlodipine day 90 vs baseline; P=0.0001, nicardipine day 90 vs baseline; P=0.0001, amlodipine 90 day change vs nicardipine 90 day change; P=0.38). Secondary: The decrease in DBP from baseline was significant within each group but similar between the groups (amlodipine day 90 vs baseline; P=0.0001; nicardipine day 90 vs baseline; P=0.0003, amlodipine 90 day change vs nicardipine 90 day change; P=0.12). The decrease in pulse pressure from baseline was significant within each group but similar between the groups (amlodipine day 90 vs baseline, P=0.0001; nicardipine day 90 vs baseline, P=0.0001; amlodipine 90 day change vs nicardipine 90 day change, P=0.88). There was no difference between the groups in heart rate (P=0.60). At day 90, 25.9, and 23.4% of the amlodipine and nicardipine groups had achieved normal blood pressure (P=0.76).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The numbers of people in each group reporting at least 1 adverse event were similar, 23 in the amlodipine group and 20 in the nicardipine group.
Kes et al.[63] (2003) Amlodipine 5 to 10 mg QD vs nifedipine 30 to 60 mg QD	MC, OL, RCT Patients with HTN	N=155 12 weeks	Primary: Change in DBP Secondary: Not reported	Primary: There was no significant difference in DBP between the amlodipine group and nifedipine group at 12 weeks (P=0.436). Secondary: Not reported
Ryuzaki et al.[64] (2007) i-TECHO Amlodipine 2.5 to 10 mg QD vs nifedipine CR 20 to 80 mg QD	OL, RCT, XO Patients treated for HTN (SBP >140 mm Hg or DBP >90 mm Hg)	N=55 12 weeks (6 weeks per treatment)	Primary: Average home blood pressure readings, pulse rates, clinic blood pressure and pulse readings Secondary: Not reported	Primary: The morning home SBP and DBP readings were lower in the nifedipine group than the amlodipine group (SBP 131±8 vs 133±10 mm Hg; P<0.05, DBP 80±8 vs 81±8 mm Hg; P<0.05). There were no significant differences in evening home blood pressure readings (P>0.05). There was no significant difference in rates of achieving target blood pressure between the groups (P<0.05). Morning home pulse rates were greater in the nifedipine group than the amlodipine group (70±9 vs 69±9 beats/min; P<0.05). There were no significant differences between the groups in evening home pulse rates (P>0.05). The clinic SBP and DBP readings were significantly lower in the nifedipine group than in the amlodipine group (P<0.05). There were no significant differences between the groups in clinic pulse rates (P>0.05). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Saito et al.[65] (2007) ADVANCE-Combi Amlodipine 2.5 to 5 mg QD vs nifedipine CR 20 to 40 mg QD Valsartan 40 to 80 mg was added on if blood pressure goal not met.	DB, RCT Patients with untreated essential HTN with sitting SBP ≥160 mm Hg or DBP ≥100 mm Hg; or previously treated with sitting SBP ≥150 mm Hg or DBP ≥95 mm Hg	N=514 16 weeks	Primary: Target blood pressure, achievement rate Secondary: Safety	Primary: Target blood pressure achievement rates were higher for the nifedipine treatment group than the amlodipine group (P<0.001). Patients in the amlodipine group were more likely to require additional treatment with valsartan or a dose increase of amlodipine (P<0.05). The reduction in blood pressure from baseline was greater in the nifedipine group (-34.0/-20.1) than in the amlodipine group (-27.0/-15.9; P<0.05). Secondary: Adverse event rates were not significantly different between the groups, 12.4% in the nifedipine group vs 7.6% of the amlodipine group (P=0.07).
Pepine et al.[66] (2003) CESNA-II Amlodipine 5 to 10 mg QD vs nisoldipine ER 20 to 40 mg QD	DB, DD, PG, MC, RCT Men and women with HTN (DBP 90-109 mm Hg) and CAD	N=not specified 6 weeks	Primary: Change from baseline in DBP at 6 weeks Secondary: Exercise duration, antihypertensive responder rate (% of patients with DBP <90 mm Hg), exercise test responder rate (increase in time by 20% and 60 seconds)	Primary: At six weeks, the mean SBP and mean DBP for the two treatment groups were not significantly different from each other and mean reductions in blood pressure were similar: amlodipine SBP/DBP 138/83 mm Hg, a decrease of 13/11 mm Hg, vs nisoldipine 137/81 mm Hg, a decrease of 15/13 mm Hg) (P values not significant). Secondary: Both treatment groups experienced increases in exercise duration, increased by 21 seconds in the amlodipine group and 23 seconds in the nisoldipine group (P=0.268). Antihypertensive and exercise responder rates were similar between the groups (antihypertensive rates: 78% for amlodipine and 87% for nisoldipine; P>0.05 for both).
Whitcomb et al.[67] (2000) Amlodipine 2.5 to	DB, DD, MC, RCT Men and women, age 21 to 75 years,	N=161 8 weeks	Primary: Between treatment comparison of change from	Primary: Treatment with amlodipine resulted in a significantly larger change from baseline in DBP (between-group difference 2.7 mm Hg; P=0.005). However, a pre-specified difference of greater than 5 mm Hg in least mean

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
10 mg QD vs nisoldipine ER 10 to 40 mg QD	with HTN		baseline in DBP Secondary: Change from baseline in SBP, heart rate, percent of patients who responded	squares, here 1.1 to 4.3 mm Hg, showed that the treatments were similar in reduction of DBP. Secondary: Amlodipine treatment resulted in a significantly larger change from baseline in SBP than nisoldipine treatment (P value not reported, least mean square difference >5 mm Hg). At week eight, more patients in the amlodipine group were responders, 79%, as compared to the nisoldipine group, 60% (P=0.004).
White et al.[68] (2003) CESNA-III Amlodipine 5 to 10 mg QD vs nisoldipine ER 20 to 60 mg QD	DB, MC, PRO, RCT African American patients with HTN (blood pressure of 92 mm Hg to 114 mm Hg and SBP <200 mm Hg)	N=192 12 weeks	Primary: ABPM change from baseline in DBP in mean 24 hour period Secondary: ABPM change in SBP, awake and asleep blood pressure, changes in clinic blood pressure and pulse	Primary: The decrease from baseline in DBP was similar between the groups: -16.0±2.3 mm Hg for nisoldipine and -15.0±2.3 mm Hg for amlodipine (P=0.500). Secondary: The decrease from baseline in SBP was similar between the groups: -23.0±2.7 mm Hg for nisoldipine and -19.9±2.7 mm Hg for amlodipine (P=0.067). The changes from baseline in awake and asleep SBP and DBP were not significantly different between the groups except for awake SBP, for which the nisoldipine group had a larger reduction, -19.2 vs -15.9 mm Hg (P=0.045). The changes from baseline in clinic blood pressure and pulse were similar between the groups (P>0.05 for SBP and DBP; P=0.362).
Lenz et al.[69] (2001) Amlodipine 5 to 10 mg QD vs nisoldipine 10 to 20 mg QD	OL, XO Patients, 35 to 70 years old, with HTN, (SBP 140 to 179 mm Hg and DBP 90 to 109 mm Hg), stable on amlodipine for ≥3 months prior to	N=21 10 weeks	Primary: 24-hr ABPM Secondary: Not reported	Primary: No significant difference in ABPM was found after patients switched from amlodipine to nisoldipine for the following: systolic nighttime, daytime and 24-hr blood pressure, diastolic nighttime and daytime blood pressure (P>0.05 for all). 24-hr DBP was significantly lower with amlodipine treatment than with nisoldipine treatment (75±10 vs 77±8.5 mm Hg; P=0.017). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	switch to nisoldipine			Not reported
Drummond et al.[70] (2007) Amlodipine 5 mg QD vs amlodipine 10 mg QD vs aliskiren and amlodipine 150-5 mg QD (fixed-dose combination product) Patients not responding to amlodipine 5 mg QD at the end of 4 week single-blind run-in period received combination therapy, continuation of amlodipine 5 mg QD or titration to amlodipine 10 mg QD.	AC, DB, MC, PG, RCT Patients 18 years of age and older with mild to moderate HTN	N=545 6 weeks	Primary: Change in DBP at 6 weeks Secondary: SBP, comparison of SBP and DBP reductions between combination therapy group and amlodipine 10 mg group, proportion of patients responding to treatment, and proportion of patients achieving blood pressure control	Primary: DBP reduction was significantly greater in the combination therapy group compared to those in the amlodipine 5 mg group (P<0.0001). Secondary: SBP reduction was significantly greater in the combination therapy group compared to those in the amlodipine 5 mg group (P<0.0001). No significant differences were observed in DBP or SBP reduction between the combination therapy group and the amlodipine 10 mg group (P=0.6167 and P=0.2666 respectively). The proportion of patients responding to treatment was significantly higher in the combination therapy group compared to the amlodipine 5 mg group (P<0.0001). No significant difference was observed between the combination therapy group and the amlodipine 10 mg group (P value not reported). The proportion of patients achieving blood pressure control was significantly higher in the combination therapy group compared to the amlodipine 5 mg group (P<0.0001). No significant difference was observed between the combination therapy group and the amlodipine 10 mg group (P=0.5229).
Benetos et al.[71] (2000)	DB, MC, PG, RCT	N=164	Primary: Changes in blood	Primary: Both bisoprolol and HCTZ and amlodipine significantly reduced SBP

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Amlodipine 5 mg QD vs bisoprolol and HCTZ 2.5-6.25 mg QD (fixed-dose combination product)	Patients over 60 years with supine SBP 160 to 210 mm Hg and DBP <90 mm Hg	12 weeks	pressure, heart rate, adverse events, QOL scores Secondary: Not reported	(-20.0±13.7 and -19.6±14.2 mm Hg, respectively; P<0.001) and DBP (-4.5±7.4 and -2.4±8.4 mm Hg, respectively from baseline to week 12, but there was not a significant difference between the agents (SBP; P=0.85 and DBP; P=0.09). Bisoprolol and HCTZ significantly reduced heart rate from baseline, but amlodipine did not (-7.6±8.4 [P<0.001] and -0.2±11.4 bpm, respectively). Bisoprolol and HCTZ significantly reduced heart rate when compared to amlodipine (P=0.0001). Overall adverse events were not significantly different between the amlodipine and the bisoprolol and HCTZ group (39 and 40%, respectively). Adverse events reported included headache, leg edema, fatigue and bradycardia but severity of events was not reported. Overall QOL scores were not significantly different between the amlodipine and the bisoprolol and HCTZ group. Secondary: Not reported
Prisant et al.[72] (1995) Amlodipine 2.5, 5, or 10 mg vs bisoprolol and HCTZ 2.5-6.25, 5-6.25, or 10-6.25 mg/day (fixed-dose combination product) vs	DB, MC, PG, RCT Patients ≥21 years with mild to moderate essential HTN, (average sitting DBP 95 to 114 mm Hg) each treatment was once daily and titrated to effect	N=218 17 weeks	Primary: Mean change from baseline in SBP and DBP, lab measurements, adverse events, QOL questionnaire Secondary: Not reported	Primary: Mean decreases in SBP and DBP from baseline were 13.4/10.7 mm Hg for bisoprolol and HCTZ patients, 12.8/10.2 mm Hg for amlodipine patients, and 7.3/6.6 mm Hg for enalapril patients. The hypotensive effects were significant for all three groups (P<0.001). SBP and DBP mean changes from baseline for the bisoprolol and HCTZ group and the amlodipine group were greater than the change from baseline for the enalapril group (P<0.01). Response rates (DBP ≤90 mm Hg or ≥10 mm Hg decrease from baseline) were 71% for the bisoprolol and HCTZ group, 69% for the amlodipine group, and 45% for the enalapril group. The response rates for the bisoprolol and HCTZ and the amlodipine groups differed significantly from the enalapril group (P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
enalapril 5, 10, or 20 mg				Twenty nine percent of bisoprolol patients had adverse experiences compared to 42% of amlodipine patients (P=0.12). Nearly 47% of enalapril patients had adverse experience compared to bisoprolol (P=0.04). Adverse events reported included headache, fatigue, peripheral edema, and dizziness. Drug related adverse events were 16% for the bisoprolol and HCTZ patients, 21% for the amlodipine patients, and 23% for the enalapril patients. There was no significant difference between the groups. Enalapril demonstrated a mean decrease from baseline of 7.9 mg/dL for TC (P=0.02 vs amlodipine) and 6.6 mg/dL for LDL-C (P=0.04 vs amlodipine) which were not significantly different from the increase from the bisoprolol and HCTZ group of 1.7 mg/dL (P=0.07 vs enalapril) for TC and +0.6 mg/dL in LDL-C. However, the increase in TGs was highest for bisoprolol and HCTZ-treated patients compared to amlodipine- and enalapril-treated patients (P=0.08, for bisoprolol and HCTZ vs enalapril). There was not a significant difference from baseline or between treatment groups in QOL scores: 0.9 for the bisoprolol and HCTZ group, 0.5 for the amlodipine group, and 2.3 for the enalapril group.
Mazza et al.[73] (2002) Amlodipine 5 to 10 mg QD vs nebivolol 2.5 to 5 mg QD	DB, MC, PG, RCT Patients between 65 to 89 years of age with mild to moderate essential HTN and DBP ranging from 95 to 114 mm Hg	N=168 16 weeks	Primary: Change in sitting blood pressure, response rates Secondary: Standing blood pressure changes, standing and sitting heart rate changes	Primary: There was not a significant difference observed between the amlodipine and nebivolol treatments groups in changes in sitting DBP (blood pressure values and P values not reported). At weeks four and eight, a slightly lower sitting SBP was observed in per-protocol patients in the amlodipine groups vs those in the nebivolol group (blood pressure values not reported, P<0.005). Response rates were not significantly difference between the amlodipine group and the nebivolol group (86 vs 88%, respectively). The percentage of patients who reached normalization (blood pressure <140/90 mm Hg) was no significant between the amlodipine and the nebivolol groups (47 vs 50%). Secondary: There were significant differences in standing blood pressure observed

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				between the groups. Heart rate was significantly lower in the nebivolol group compared to the amlodipine group at all treatment visits (P<0.001). Patients in the amlodipine group experienced a significantly greater rate of headache (seven vs five patients) and ankle edema (12 vs zero patients) compared to the patients in the nebivolol group (P<0.05 for both).
Hollenberg et al.[74] (2003) Amlodipine 2.5 mg/day vs eplerenone 50 mg/day Both medications were titrated to a maximum of 200 (eplerenone) or 10 (amlodipine) mg/day to achieve a SBP<140 mm Hg.	RCT Patients ≥50 years of age, with untreated SBP between 140 to 190 mm Hg	N=269 24 weeks	Primary: Change in SBP and DBP, discontinuation rate, symptom distress index, SF-36 Health Survey Secondary: Not reported	Primary: Both treatments exhibited similar reductions in SBP and DBP from baseline (P=0.01). The dropout rate was 50% greater in amlodipine-treated patients compared to eplerenone-treated patients (P value not reported). Symptom distress (technique used to assess the influence of drug treatment on QOL) index was assessed and results favored eplerenone therapy (P=0.03). SF-36 Health Survey showed no significant difference between the two treatments (P value not reported). Both treatments experienced similar incidences of adverse effects (P value not reported). Eplerenone-treated patients did not experience breast pain/tenderness, breast enlargement, changes in menstruation, gynecomastia or loss of libido. Secondary: Not reported
White et al.[75] (2003) Amlodipine 2.5 mg/day vs	AC, DB, MC, RCT Patients ≥50 years of age with systolic HTN (seated clinic SBP 150 to 165 mm Hg with a pulse pressure ≥70 mm	N=269 24 weeks	Primary: Mean change from baseline in SBP, DBP, 24 hour ambulatory BP, pulse pressure, and heart rate at week 24; urine albumin/	Primary: Mean reduction in SBP from baseline was comparable in eplerenone- and amlodipine-treated patients (P=0.83). Eplerenone-treated patients exhibited significant reductions in DBP from baseline at 24 weeks of therapy compared to amlodipine-treated patients (P=0.014).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
eplerenone 50 mg/day Both medications were titrated to a maximum of 200 (eplerenone) or 10 (amlodipine) mg/day to achieve a SBP<140 mm Hg.	Hg or 165 to 200 mm Hg with a DBP ≤95 mm Hg)		creatinine ratio; adverse events Secondary: Not reported	The two treatments exhibited comparable decreases in 24 hour ambulatory BP, pulse pressure and heart rate after 24 weeks of therapy (P>0.05). Eplerenone-treated patients exhibited a significant reduction from baseline in the urine albumin/creatinine ratio compared to amlodipine-treated patients (P=0.002). Treatment-emergent adverse events were reported in 64 and 70% of eplerenone- and amlodipine-treated patients. The only adverse event that was significant between the two treatments was the incidence of edema (3.7 vs 25.5%; P<0.05). There were no reports of gynecomastia, breast tenderness or menstrual irregularities with either treatment. Secondary: Not reported
Jordan et al.[76] (2007) Amlodipine 5 to 10 mg QD, added to existing HCTZ therapy (single entity products) vs aliskiren 150 to 300 mg QD, added to existing HCTZ therapy (single entity products) vs irbesartan 150 to 300 mg QD, added to existing HCTZ	DB, DD, MC, PG, RCT Obese men and women (BMI ≥30 kg/m^2) ≥18 years with essential HTN (mean sitting DBP 95 to 109 mm Hg and SBP <180 mm Hg) who had not responded to 4 weeks of treatment with HCTZ 25 mg	N=489 12 weeks	Primary: Change in mean sitting DBP with aliskiren 300 mg plus HCTZ vs HCTZ alone at 8 weeks Secondary: Comparisons of mean sitting DBP and SBP with aliskiren plus HCTZ vs the other treatment groups, percentage of responders (mean sitting DBP <90 mm Hg or ≥10 mm Hg reduction from baseline), proportion of	Primary: Aliskiren 300 mg added to HCTZ 25 mg significantly reduced mean sitting DBP compared to HCTZ alone at week eight (mean difference, -4.0; P<0.0001). Secondary: Aliskiren 300 mg added to HCTZ caused numerically larger reductions in mean sitting DBP and SBP compared to amlodipine 10 mg plus HCTZ and irbesartan 300 mg plus HCTZ at week eight, but there were no statistically significant differences between treatment groups (P>0.05). Responder rates were significantly higher with aliskiren plus HCTZ than HCTZ alone at week eight (P=0.0193) and week 12 (P=0.004) but comparable to responder rates observed with amlodipine plus HCTZ (P>0.05) and irbesartan plus HCTZ (P>0.05). The proportion of patients achieving blood pressure control was significantly higher with aliskiren plus HCTZ than HCTZ alone at week eight (P=0.0005) and week 12 (P=0.0001) but not statistically different than amlodipine plus HCTZ (P>0.05) and irbesartan plus HCTZ (P>0.05). Plasma renin activity significantly increased (P<0.05) during four weeks

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
therapy (single entity products) vs HCTZ 25 mg QD (existing therapy)			patients achieving blood pressure control (mean sitting blood pressure <140/90 mm Hg), plasma renin activity, safety and tolerability	of HCTZ monotherapy. Combination with aliskiren neutralized this increase and led to an overall significant reduction in plasma renin activity compared to pretreatment baseline (P<0.05) whereas amlodipine and irbesartan led to further significant increases (P<0.05). All of the study treatments were generally well tolerated. Amlodipine plus HCTZ (45.2%) was associated with a higher incidence of adverse events than the other treatment groups (36.1 to 39.3%), largely due to a higher rate of peripheral edema (11.1 vs 0.8 to 1.6%).
Sundström et al.[77] (2023) Amlodipine 10 mg vs candesartan 16 mg vs lisinopril 20 mg vs HCTZ 25 mg Half doses given weeks 1 and 2 of each treatment period, and full doses weeks 3 through 9	DB, PRO, XO, RCT Patients aged 40 to 75 years previously diagnosed with HTN, with SBP 140 to 159 mmHg within a five-year period prior to the start of the trial and SBP 140 to 179 mm Hg and DBP ≤109 mm Hg at the randomization visit Patients were pharmacologically untreated or used BP-lowering monotherapy at the inclusion visit	N=280 Six treatment periods, each being 7 to 9 weeks in duration, after a 2 week washout period; 1-week washout periods between each treatment period	Primary: Ambulatory daytime SBP at the end of each treatment period Secondary: Not reported	Primary: Participants had higher BP when taking HCTZ than when taking other treatments, when taking amlodipine compared with lisinopril, and when taking candesartan compared with lisinopril The blood pressure response to different treatments varied considerably between individuals (P<0.001), specifically for the choices of lisinopril vs hydrochlorothiazide, lisinopril vs amlodipine, candesartan vs hydrochlorothiazide, and candesartan vs amlodipine. On average, personalized treatment had the potential to provide an additional 4.4 mm Hg–lower systolic blood pressure. Secondary: Not reported
Messerli et al.[78] (2002) Amlodipine and benazepril 5-10 mg	OL Patients ≥18 years with mild-to-moderate HTN	N=7,912 4 weeks	Primary: Change in mean sitting DBP (group 1), and percentage of patients whose	Primary: In Group 1, mean reduction in DBP at week four was 11.5 mm Hg (95% CI, -11.8 to -11.3 mm Hg; P<0.001). Mean DBP declined from 96.5 (baseline) to 84.9 mm Hg (at 4 weeks).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
to 5-20 mg QD (fixed-dose combination product)	taking amlodipine 5 to 10 mg with inadequate blood pressure (DBP ≥90 mm Hg, Group 1) or intolerance with amlodipine (DBP ≤90 mm Hg with edema, Group 2)		edema improved (group 2) Secondary: Group 1-change in mean sitting SBP	In Group 2, 85% of patients saw improvement in edema with 42% of patients experiencing complete resolution after receiving combination therapy (95% CI, 83 to 87). Secondary: In Group 1, mean reduction in SBP at week four was 15.6 mm Hg (95% CI, -16.0 to -15.2 mm Hg; P<0.001).
Chrysant et al.[79] (2012) Study 1: Benazepril 40 mg/day (Group 1) vs amlodipine and benazepril 5-40 mg/day, up titrated to 10-40 mg/day after 4 weeks. (fixed-dose combination product) (Group 2) Study 2: Amlodipine and benazepril 10-20 mg/day, uptitrated to 10-40 mg/day after 2 weeks (Group 3) vs amlodipine and	Post-hoc analysis of 2 trials Patients with HTN	N=1,013 14 weeks	Primary: Change in baseline mean sitting DBP and mean sitting SBP, rate of blood pressure control (<140/90 mm Hg), rate of blood pressure control (mean sitting DBP <90 mm Hg or ≥10 mm Hg decrease from baseline) Secondary: Safety	Primary: Pooled results demonstrate that combination therapy resulted in significantly greater lowering of mean sitting DBP and mean seated SBP compared to benazepril or amlodipine (P<0.001). Amlodipine and benazepril 10-20 mg/day resulted in significantly greater blood pressure reductions in White patients (mean sitting DBP: 12.99 mm Hg; mean sitting SBP: 13.72 mm Hg) compared to Black patients (8.80 and 8.72 mm Hg) (P<0.004). Amlodipine and benazepril 10-40 mg/day resulted in similar reductions in blood pressure in both White and Black patients. The proportion of patients who achieved blood pressure control with amlodipine and benazepril 10-40 mg/day was similar between White and Black patients (60.7%), whereas with amlodipine and benazepril 10-20 mg/day the rate of control was higher with White patients (61.2 vs 39.4%; P<0.023). There was no difference in the proportion of patients who responded to treatment between Black and White patients with amlodipine and benazepril 10-40 mg/day (74.8 vs 77%; P<0.639). The proportion of patients who responded to amlodipine and benazepril 10-20 mg/day was significantly lower in Black patients (50.7 vs 73.5%; P<0.007). Secondary: There were no serious clinical or metabolic side effects reported, with the exception of pedal edema which occurred more frequently with amlodipine monotherapy.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
benazepril 10-20 mg/day (fixed-dose combination product) (Group 4) vs amlodipine 10 mg/day (Group 5)				
Messerli et al.[80] (2000) <u>Study 1:</u> Amlodipine and benazepril 5-10 mg to 5-20 mg QD (fixed-dose combination product) vs nifedipine 30 to 60 mg/day <u>Study 2:</u> Amlodipine and benazepril 5-10 mg to 5-20 mg QD (fixed-dose combination product) vs amlodipine 5 to 10 mg QD	2 DB, MC, RCT Patients 18 to 80 years of age with uncomplicated essential HTN	N=1,079 8 weeks	Primary: Change in DBP from baseline Secondary: Change from baseline in SBP and heart rate	Primary: Study 1 Significant reductions in DBP were observed with benazepril and amlodipine 10-5 and 20-5 mg (-9.4 and -9.7 mm Hg, respectively) compared to nifedipine 30 mg (-7.0 mm Hg; P<0.05), but not nifedipine 60 mg (-8.5; P>0.05). Study 2 Benazepril and amlodipine 10-5 (-8.9 mm Hg) and 20-5 mg (-9.1 mm Hg) produced significantly greater reductions in DBP than amlodipine 5 mg (-6.8 mm Hg; P<0.05), but not amlodipine 10 mg (-8.7 mm Hg; P>0.05). Secondary: Study 1 Significant reductions in SBP were observed with benazepril and amlodipine 20-5 mg (-11.6 mm Hg) compared to nifedipine 30 mg (-7.9 mm Hg; P<0.05). Significantly less edema was reported with combination therapies (3.1 to 3.8%; P≤0.001) compared to nifedipine 60 mg (15.5%; P=0.008) but not nifedipine 30 mg (5.4%). Study 2 Significant reductions in SBP were observed with benazepril and amlodipine 20-5 mg (-9.1 mm Hg) compared to amlodipine 5 mg (-5.3 mm Hg; P<0.05). There were no significant difference in SBP between amlodipine 10 mg and the combination therapies.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Significantly less edema (P<0.001) was reported with amlodipine 5 mg (4.9%) and combination therapies (1.5 to 2.2%) compared to amlodipine 10 mg (23.6%).
Jamerson et al.[81] (2004) Amlodipine and benazepril 5-20 and 10-20 mg/day (fixed-dose combination product) vs amlodipine 5 to 10 mg/day	DB, MC, PG, RCT Men and women 18 to 80 years of age with stage 2 HTN	N=364 12 weeks	Primary: Percentage of patients with SBP reduction ≥25 mm Hg (if baseline <180 mm Hg) or ≥32 mm Hg (if baseline ≥180 mm Hg) Secondary: Percentage of patients with DBP reduction ≥15 mm Hg (if baseline <110 mm Hg) or ≥20 mm Hg (if baseline ≥110 mm Hg), percentage of patients meeting goal of 140/90 and ≤130/85 mm Hg, mean reduction in SBP and DBP and incidence of edema	Primary: Significantly more patients on combination therapy (74.2%) met the primary end point than patients on amlodipine monotherapy (53.9%; P<0.0001). The time by which 50% of patients attained the primary end point was four weeks shorter among patients randomized to combination therapy compared to those randomized to monotherapy (P<0.0001). Secondary: Significantly more patients on combination therapy met the DBP end point than patients on amlodipine monotherapy (67.0 vs 48.3%; P=0.0003). Patients on combination therapy had significantly greater mean SBP reductions (-25.5 vs -20.5 mm Hg; P=0.0003) and DBP reductions (-14.3 vs -10.4 mm Hg; P=0.0001) than patients on amlodipine monotherapy. Significantly more patients on combination therapy met the BP goal of <140/90 mm Hg than patients on amlodipine monotherapy (61.0 vs 43.3%; P=0.0007). Significantly more patients on combination therapy met the BP goal of <130/85 mm Hg than patients on amlodipine monotherapy (35.7 vs 19.1%; P=0.0004). The incidence of peripheral edema was significantly higher in the amlodipine monotherapy group (23.3 vs 12.6%; P=0.0102). There was no significant difference in the incidence of other adverse events.
Neutel et al.[82] (2005) SELECT Amlodipine and benazepril 5-20	DB, RCT Patients with stage 2 systolic HTN	N=443 8 weeks	Primary: Reduction in SBP, proportion of patients achieving blood pressure control	Primary: Significantly greater SBP reductions were achieved with combination therapy compared to amlodipine or benazepril monotherapy (P<0.0001). Significantly more patients on combination therapy met blood pressure goals than on monotherapy (P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day (fixed-dose combination product) vs amlodipine 5 mg/day vs benazepril 20 mg/day			Secondary: Not reported	No significant difference was noted in the incidence of adverse events. Adverse events were low in all three treatment arms, with less peripheral edema in the combination group than in the amlodipine-treated group. Secondary: Not reported
Kuschnir et al.[83] (1996) Amlodipine-benazepril 5/20 mg QD (fixed-dose combination) vs amlodipine 5 mg QD vs benazepril 20 mg QD vs placebo	DB, MC, PC, PG, RCT Men and women 21 to 80 years of age with uncomplicated primary HTN	N=308 8 weeks	Primary: Reduction in mean sitting DBP, SBP and percentage of patients with DBP <90 mm Hg or ≥10 mm Hg reduction	Primary: All treatment groups significantly reduced mean sitting DBP compared to placebo (P<0.001). Combination amlodipine/benazepril had significantly greater reductions in DBP (-13.2 mm Hg; P<0.001) compared to amlodipine (-8.8 mm Hg) and benazepril (–6.7 mm Hg) monotherapy. Combination amlodipine and benazepril had significantly greater reductions in SBP (-24.7 mm Hg; P<0.001) compared to amlodipine (-16.2 mm Hg) and benazepril (-12.4 mm Hg). Significantly more patients on combination amlodipine and benazepril reached DBP <90 mm Hg or ≥10 mm Hg reduction (87.0%; P≤0.005) compared to amlodipine (67.5%) and benazepril (53.3%). Adverse events considered to be drug related occurred in 15.6% of patients receiving amlodipine and benazepril, 24.7% of patients receiving amlodipine, 6.5% of patients on benazepril and 11.7% of patients on placebo.
Chrysant et al.[84] (2007)	DB, MC, RCT Men and women	N=812 6 weeks	Primary: Reduction in mean sitting DBP and	Primary: Treatment with benazepril 40 mg and amlodipine 10 and benazepril 20 mg and amlodipine 10 mg resulted in a decrease of mean sitting SBP and DBP

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Amlodipine and benazepril 10-40 mg QD for 6 weeks (fixed-dose combination product) vs amlodipine and benazepril 10-40 mg QD for 2 weeks, followed by 20-40 mg QD for 4 weeks (fixed-dose combination product) vs amlodipine 10 mg QD for 6 weeks	≥18 years of age with mean sitting DBP ≥95 mm Hg not adequately controlled with amlodipine 10 mg/day monotherapy		SBP, reductions in ambulatory blood pressure, successful response (mean sitting DBP <90 mm Hg or decrease of ≥10 mm Hg from baseline), safety Secondary: Not reported	by 13.3/12.7 and 12.1/11.6 mm Hg, respectively, compared to monotherapy (6.6/8.5 mm Hg; P<0.0001). Benazepril 40 mg and amlodipine 10 mg and benazepril 40 mg and amlodipine 20 mg decreased ambulatory SBP and DBP by 9.9/6.7 and 7.4/5.2 mm Hg, respectively, compared to monotherapy (P<0.0001). Both combination therapy groups resulted in more responders than monotherapy (74 and 65 vs 54%; P<0.0001 and P<0.0085, respectively). Combination therapy had significantly greater reductions in sitting SBP (-17 mm Hg; P<0.0001) compared to amlodipine monotherapy (-5 mm Hg). The incidence of pedal edema was lower but not significantly different in the combination therapy groups compared to monotherapy (4.5, 5.5 vs 9.2%, respectively; P value not significant). No significant metabolic side effects were noted among the combination therapy groups. Secondary: Not reported
Chrysant et al.[85] (2004) Amlodipine and benazepril 5-40 mg QD for 4 weeks, followed by 10-40 mg QD for 4 weeks (fixed-dose combination product) vs benazepril 40 mg	DB, RCT Men and women (mean age 53 years) with mean sitting DBP ≥95 mm Hg not adequately controlled with benazepril 40 mg/day monotherapy	N=329 8 weeks	Primary: Reduction in mean sitting DBP and SBP, reduction in standing DBP and SBP, and change in heart rate, safety Secondary: Not reported	Primary: Combination therapy had significantly greater reductions in sitting SBP (-17 mm Hg; P<0.0001) compared monotherapy (-5 mm Hg). Combination therapy had significantly greater reductions in sitting DBP (-14 mm Hg; P<0.0001) compared to monotherapy (-7 mm Hg). Combination therapy had significantly greater reductions in standing SBP (-17 mm Hg; P<0.0001) compared to monotherapy (-6 mm Hg). Combination therapy had significantly greater reductions in standing DBP (-14 mm Hg; P<0.0001) compared to monotherapy (-7 mm Hg). No significant differences in heart rate were observed (P>0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD for 8 weeks				No significant differences in adverse events were reported (P>0.05). Secondary: Not reported
Fogari et al.[86] (1997) Amlodipine and benazepril 2.5-10 to 5-10 mg QD (fixed-dose combination product) vs benazepril 10 mg QD	DB, MC, PC, RCT Men and women 24 to 73 years of age (mean 55 years) with HTN inadequately controlled with ACE inhibitor monotherapy	N=448 8 weeks	Primary: Reduction in mean sitting DBP Secondary: Reduction in sitting SBP, standing DBP and SBP, and percentage of patients with DBP <90 mm Hg (deemed excellent response) or a ≥10 mm Hg reduction (deemed good response)	Primary: Significantly greater reductions in sitting DBP were observed with benazepril 10 mg and amlodipine 2.5 mg (-5.3 mm Hg, 97.5% CI, -8.3 to -2.4; P=0.0001) and benazepril 10 mg and amlodipine 5 mg (-4.5 mm Hg, 97.5% CI, -7.4 to -1.6; P=0.0006) compared to benazepril monotherapy. Secondary: Significantly greater reductions in sitting SBP were seen with benazepril 10 mg and amlodipine 2.5 mg (-7.9 mm Hg, 97.5% CI, -12.3 to -3.5; P=0.0001) and benazepril 10 mg and amlodipine 5 mg (-7.9 mm Hg, 97.5% CI, -12.2 to -3.6; P=0.0000) compared to benazepril monotherapy. Significantly greater reductions in standing DBP and SBP were also reported with the combination therapy compared to benazepril monotherapy (P≤0.001). Significantly more patients had excellent or good response with benazepril 10 mg and amlodipine 2.5 mg (69.2%; P=0.0004) and 10-5 mg (65.8%; P=0.02) compared to benazepril monotherapy (40.5%). Tolerability was good in the three treatment groups and no significant abnormal laboratory data was detected.
Minami et al.[87] (2007) Losartan 50 mg/day and HCTZ 12.5 mg/day vs candesartan 8 mg QD or amlodipine 5	OL Japanese outpatients with essential HTN treated for ≥2 months with either candesartan or amlodipine and 24-hour ambulatory blood pressure ≥135/80 mm Hg	N=15 12 months	Primary: Changes in blood pressure Secondary: Not reported	Primary: In patients who had previously received candesartan, 24-hr blood pressure decreased significantly from 137/89 mm Hg to 126/81 mm Hg after three months (P<0.05/P<0.001) and to 123/81 mm Hg after 12 months (P<0.01/P<0.001) of treatment with losartan and HCTZ. In patients who had previously received amlodipine, 24-hr blood pressure decreased significantly from 137/81 to 125/75 mm Hg after three months (P<0.05/P<0.05) and to 124/77 mm Hg after 12 months (P<0.05/P value not significant) of treatment with losartan and HCTZ.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg QD				There were significant decreases in SBP during the daytime, nighttime and early morning after 12 months in both groups. No adverse changes in the indices of glucose or lipid metabolism were observed in either group. Secondary: Not reported
Hilleman et al.[88] (1999) Amlodipine-benazepril (fixed-dose combination) vs monotherapy (atenolol, HCTZ, captopril, enalapril, lisinopril, amlodipine, diltiazem, nifedipine, verapamil)	MA Patients with mild-to-moderate essential hypertension	82 trials ≥4 weeks	Primary: Absolute change in supine DBP from baseline Secondary: Percent of patients who achieved blood pressure control, safety	Primary: The mean absolute decrease in supine DBP ranged from 9.7 to 13.3 mm Hg with verapamil showing the greatest effect and captopril the least. When studies were weighted by sample size, amlodipine and benazepril, atenolol, lisinopril, and verapamil showed the greatest blood pressure effect. Secondary: The average percentage of patients defined as controlled after treatment varied from 53.5 to 79.0%, with amlodipine and benazepril (74.3%) and lisinopril (79.0%) showing the highest percentage control (P=0.096). The incidence of adverse events ranged from 12.1 to 41.8%, with lisinopril and verapamil showing the lowest incidences (12.1% and 14.1%, respectively) and nifedipine the highest incidence. Lisinopril demonstrated significantly less overall side effects compared to nifedipine (P=0.030). Nifedipine demonstrated a higher withdrawal rate due to side effects compared to atenolol, HCTZ, enalapril, amlodipine, and diltiazem (P=0.002). Although amlodipine and benazepril had the lowest rate of withdrawals due to adverse events, lack of significant change was due to the low number of cohorts available for analysis.
Jamerson et al.[89] (2007) ACCOMPLISH Amlodipine 5 mg QD plus benazepril 20 mg QD	DB, MC, RCT Patients >60 years of age with HTN and at high risk of cardiovascular events	N=10,704 Analysis performed at 6 months (complete trial duration 5	Primary: Changes in mean SBP from baseline to 6 months, blood pressure control rates (SBP/DBP <140/90 mm Hg or	Primary: At baseline, 97% of subjects were treated with antihypertensive medications at entry, but only 37% of participants had blood pressure control. Mean blood pressure fell from 145/80 to 132/74 mm Hg after six months of treatment with either combination regimen (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs benazepril 20 mg QD plus HCTZ 12.5 mg QD		years)	<130/89 mm Hg for patients with diabetes and chronic kidney disease) Secondary: Not reported	The six month blood pressure control rate was 73% in the overall trial (78% in the United States), 43% in diabetics, and 40% in patients with renal disease. Of the patients uncontrolled, 61% were not on maximal medications. Secondary: Not reported
Malacco et al.[90] (2002) Amlodipine and benazepril 5-10 mg QD (fixed-dose combination product) vs captopril and HCTZ 50-25 mg QD (fixed-dose combination product)	DB, MC, RCT Patients with mild to moderate arterial HTN (sitting DBP >95 mm Hg and/or SBP >160 mm Hg) inadequately controlled by monotherapy with an ACE inhibitor, calcium-channel blocking agent or diuretic	N=397 12 weeks	Primary: Reduction in sitting DBP and SBP Secondary: Percentage of patients responding to therapy (DBP<90 mm Hg, reduction in DBP ≥10 mm Hg or SBP ≥20 mm Hg, or SBP <150 mm Hg)	Primary: Significantly lower sitting DBP (-2.7 mm Hg; P<0.001) and SBP (-3.7 mm Hg; P<0.001) were achieved with amlodipine and benazepril compared to captopril and HCTZ. Secondary: Significantly more amlodipine and benazepril patients responded to therapy (94.8%) compared to captopril and HCTZ (86.0%; P=0.004). No differences in adverse events were reported between the two treatment groups.
Kereiakes et al.[91] (2007) Benazepril 10 mg/day for 2 weeks, then 20 mg/day for 2 weeks, then benazepril 20 mg/day plus amlodipine 5 mg/day for 4 weeks, then benazepril 20	DB, DD, MC, PG, RCT Patients with stage 2 HTN	N=190 12 weeks	Primary: Change in mean seated SBP at the end of week 12 Secondary: DBP at the end of week 12, percent of patients attaining blood pressure goals of <140/90, <130/85,	Primary: Patients treated with olmesartan and HCTZ experienced significantly greater reductions in mean seated SBP at week 12 than patients treated with benazepril plus amlodipine (least square mean change, -32.5 vs -26.5 mm Hg; P=0.024; least square mean treatment difference, -6.0 mm Hg; 95% CI, -11.1 to -0.8). Secondary: The least square mean change for reduction in DBP approached statistical significance with olmesartan and HCTZ compared to benazepril plus amlodipine at week 12 (P=0.056).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day plus amlodipine 10 mg/day for 4 weeks vs olmesartan 20 mg/day for 2 weeks, then 40 mg/day for 2 weeks then olmesartan and HCTZ 40-12.5 mg/day for 4 weeks increased to 40-25 mg for 4 weeks			and <130/80 mm Hg	The percentage of patients achieving goal rates at the end of the study for olmesartan and HCTZ and benazepril plus amlodipine were 66.3 and 44.7% (P=0.006) for <140/90 mm Hg, 44.9 vs 21.2% (P=0.001) for <130/85 mm Hg, and 32.6 and 14.1% (P=0.006) for <130/80 mm Hg. Both treatments were well tolerated.
Tatti et al.[92] (1998) FACET Amlodipine 10 mg QD vs fosinopril 20 mg QD If blood pressure was not controlled on monotherapy, the other study drug was added.	OL, PRO, RCT Men and women, diagnosed with HTN (SBP >140 mm Hg or DBP >90 mm Hg) and non-insulin dependent diabetes	N=380 Up to 3.5 years	Primary: Blood pressure Secondary: Fasting serum glucose, serum creatinine, plasma insulin, HbA_{1c}, TC, HDL-C, TG, fibrinogen, microalbuminuria	Primary: Both treatment groups significantly lowered SBP and DBP from baseline (P<0.05). SBP was lower in the amlodipine group by 4 mm Hg than in the fosinopril group (P<0.01). There was no difference in DBP, both groups decreased by 8 mm Hg. Amlodipine was added by 30.7% of the fosinopril group and fosinopril was added by 26.2% of the amlodipine group (P>0.1). Secondary: No difference between the groups was found for serum creatinine, HbA_{1c}, and triglycerides at the endpoint (P>0.05). Fasting serum glucose, serum insulin and microalbuminuria were significantly lower at endpoint for both groups but not significantly different from each other (P>0.05). Total cholesterol increased in both groups, and high-density lipoprotein cholesterol increased significantly in the fosinopril group (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				No difference in fibrinogen levels was observed between the groups at the end of the trial (P>0.05).
Miranda et al.[93] (2008) Amlodipine 2.5 to 10 mg and ramipril 2.5 to 10 mg QD vs amlodipine 2.5 to 10 mg QD	AC, DB, MC, RCT Adults 40 to 79 years of age with stage 1 or 2 essential HTN	N=222 18 weeks	Primary: Change in SBP and DBP Secondary: Safety and tolerability	Primary: The mean changes in ambulatory BP were greater with amlodipine and ramipril compared to amlodipine monotherapy (SBP, -20.21 vs -15.31 mm Hg and DBP, -11.61 vs -8.42 mm Hg, respectively; both, P=0.002]. There was no significant difference among the treatment groups in office BP (SBP, -26.60 vs -22.97 mm Hg and DBP, -16.48 vs -14.48 mm Hg; both, P value not significant). Secondary: Twenty-nine patients (22.1%) treated with combination therapy and 41 patients (30.6%) treated with monotherapy experienced ≥1 adverse event considered possibly related to study drug. The combination-therapy group had lower prevalence of edema (7.6 vs 18.7%; P=0.011) and a similar prevalence of dry cough (3.8 vs 0.8%; P value not significant).
Fogari et al.[94] (2007) CANDIA Amlodipine 10 mg QD vs candesartan 16 mg and HCTZ 12.5 mg QD	DB, MC, RCT Patients, 20 to 80 years old, with mild to moderate uncomplicated HTN not controlled on monotherapy with an antihypertensive (SBP <180 mg Hg and DBP 90 to 110 mg Hg)	N=203 8 weeks	Primary: Decrease in DBP Secondary: Sitting SBP, reduction of the orthostatic blood pressure at least two minutes after standing, change in heart rate, percentage of patients normalized (DBP <90 mm Hg and SBP <140 mm Hg), percentage of responders (reduction in DBP ≥5 mm Hg)	Primary: There was no significant difference in the mean decrease in DBP between treatment groups; the difference in final DBP was -0.02 mm Hg (95% CI, -1.48 to 1.52f; P=0.979). Secondary: There was no significant difference between the groups at week eight for the following: sitting SBP (P=0.835), heart rate (P<0.500), orthostatic SBP (P=0.883), orthostatic DBP (P=0.264), percentage of patients normalized (P=10), percentage of responders (P=0.900). The number of patients reporting an adverse event was greater in the amlodipine group (P=0.001). The number of patients reporting an adverse drug-related event was greater in the amlodipine group (P<0.001). Changes in blood chemistry and other secondary measurements were not significantly different between the treatment groups.
Ribeiro et al.[95]	DB, DD, RCT	N=194	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2007) LAMHYST Amlodipine 5 to 10 mg QD vs losartan 50 to 100 mg QD	Males and females, age 18 to 79 years old, with diagnosis of mild (>95 mm Hg but <115 mm Hg) to moderate essential HTN and not taking an antihypertensive medication (within last 4 weeks)	12 weeks	Difference between treatment groups in mean change in ABPM for last 9 hours of treatment and during drug holiday Secondary: Not reported	After 12 weeks, mean reductions in SBP were significantly larger in the amlodipine group than the losartan group (-18.1 vs -10.1 mm Hg; P<0.001). Mean reductions in DBP were significantly larger in the amlodipine group than the losartan group (-18.1 vs -10.1 mm Hg; P<0.05). Mean increases in SBP were similar between the groups during the two day drug holiday (P>0.05). After the two day drug holiday, SBP was lower than baseline in both groups (P<0.001), with the amlodipine group SBP remaining significantly lower (P<0.01). Mean increases in DBP were similar between the groups during the two day drug holiday (P>0.05). After the two day drug holiday, DBP was lower than baseline in both groups (P=0.0001), with the amlodipine group DBP remaining significantly lower (P<0.05). Secondary: Not reported
Oparil et al.[96] (1996) Amlodipine 5 to 10 mg QD vs losartan 50 to 100 mg QD If goal DBP (≤90 mm Hg) was not attained, drug doses could be doubled and/or HCTZ mg was added.	DB, DD, MC, RCT Patients with HTN	N=900 12 weeks	Primary: Efficacy, tolerability, effects on QOL Secondary: Not reported	Primary: DBP reductions after 4, 8, and 12 weeks of therapy were clinically comparable (losartan group: 7.3, 10.4, and 11.1 mm Hg, respectively; amlodipine group: 7.9, 11.2, and 11.8 mm Hg, respectively; P value not significant). Similar reductions in SBP were seen for both treatment groups (P value not significant). The percentage of patients reaching goal DBP (≤90 mm Hg) or DBP ≥90 mm Hg with a ≥10 mm Hg decrease from baseline) was comparable for the two groups, with 68% of patients in the losartan group and 71% of patients in the amlodipine group reaching goal. Significantly more patients in the amlodipine group had drug-related adverse experiences (27 vs 13%; P=0.029). Edema was more common in patients receiving the amlodipine regimen than in those receiving the losartan regimen (11 vs 1%; P=0.004).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Overall QOL was not different in the two treatment groups. Secondary: Not reported
Chrysant et al.[97] (2008) COACH Amlodipine 5 to 10 mg QD and olmesartan 10 to 40 mg vs amlodipine 5 to 10 mg QD vs olmesartan 10 to 40 mg QD vs placebo	DB, MC, PC, RCT Patients, age 18 years and older, with seated DBP of 95 to 120 mm Hg	N=1,940 8 weeks	Primary: Change from baseline in seated DBP at week 8 Secondary: Change from baseline in seated SBP at week 8; mean change from baseline in seated DBP and SBP at weeks 2, 4, 6 and 8 without last observation carried forward; proportion of patients achieving blood pressure goal (<140/90 mm Hg or <130/80 mm Hg); safety	Primary: All active treatments and placebo resulted in significant decreases in seated DBP at week eight (P<0.001). Reductions in seated DBP with monotherapy treatment ranged from -8.3 to -12.7 mm Hg; reductions with combination therapy ranged from -13.8 to -19.0 mm Hg. All combinations reduced seated DBP significantly greater than either component as monotherapy at the same dosage (P<0.001). Secondary: All active treatments and placebo resulted in significant decreases in seated SBP at week eight (P<0.001 for treatment, P=0.024 for placebo). All combinations reduced seated SBP significantly greater either component as monotherapy at the same dosage (P<0.001). The proportion of patients achieving goal blood pressures were: 20.0 to 36.3% of patients receiving olmesartan monotherapy, 21.1 to 32.5% of patients receiving amlodipine monotherapy, 35.0 to 53.2% of patients receiving combination therapy, and 8.8% of patients receiving placebo. Combination therapy resulted in significantly greater achievement of goal blood pressure than monotherapy (P<0.005). No difference in overall rates of adverse events across the different treatment groups was seen. Nearly 27% of patients experienced a drug-related adverse event. Changes in laboratory values were not considered clinically significant nor followed a consistent pattern with treatment: none of the changes were considered clinically significant. Platelet counts increased significantly from baseline (statistically) for patients receiving amlodipine, however the increase was <10% and not deemed clinically relevant.
Chrysant et al.[98]	OL, ES	N=1,684	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2009) COACH Amlodipine 5 to 10 mg QD and olmesartan 10 to 40 mg HCTZ 12.5 to 25 mg could be added if blood pressure was not controlled (<140/90 mm Hg or <130/80 mm Hg in patients with diabetes).	Patients ≥ 18 years of age with essential HTN (seated DBP ≥95and <120 mm Hg)	44 weeks OL therapy (52 weeks total study duration including 8 week DB phase)	Reduction in mean sitting SBP DBP, change in mean sitting SBP and DBP, percentage of patients achieving blood pressure goal (<140/90 mm Hg or <130/80 mm Hg for patients with diabetes)	Mean sitting DBP decreased from 101.5 mm Hg at baseline to 81.9 mm Hg and mean sitting SBP decreased from 163.6 mm Hg at baseline to 131.2 mm Hg at week 52. Approximately 31% of patients remained on amlodipine 5 mg and olmesartan 40 mg. Increasing the dose of amlodipine to 10 mg in combination with olmesartan 40 mg produced further decreases in mean sitting DBP of 4.8 mm Hg and mean sitting SBP of 7.3 mm Hg. Addition of HCTZ 12.5 mg to amlodipine 10 mg and olmesartan 40 mg decreased mean sitting DBP by 4.5 mm Hg and mean sitting SBP by 7.7 mm Hg. Doubling the HCTZ dose from 12.5 to 25 mg decreased mean sitting DBP and mean sitting SBP by an additional 6.0 mm Hg and 9.9 mm Hg, respectively. Patients who received the triple therapy had the greatest mean sitting SBP reduction (36.1 mm Hg). Approximately 67% of patients achieved blood pressure goal by week 52. The blood pressure goal achievement was 80% for amlodipine and olmesartan 5/40 mg, 70.6% for amlodipine and olmesartan 10/40 mg, 66.6% for amlodipine and olmesartan and HCTZ 10/40/12.5 mg, and 46.3% for amlodipine and olmesartan and HCTZ 10/40/25 mg. The addition of HCTZ 25 mg enabled more patients to achieve blood pressure targets of <140/90 mm Hg (77.7%), <130/85 mm Hg (47.5%), and <130/80 mm Hg (36.4%) compared to the other treatment regimens. No major safety issues emerged with long-term therapy. The frequency of edema ranged from 8.9% in patients treated with amlodipine 5 mg and olmesartan 40 mg to 14.5% in patients treated with amlodipine 10 mg and olmesartan 40 mg plus HCTZ 25 mg. Other treatment-emergent adverse events experienced by ≥3% of patients included upper respiratory tract infection (6.5%), nasopharyngitis (5.2%), extremity pain (4.1%), sinusitis (3.6%), arthralgia (3.3%), and back pain (3.1%). headache (2.0%), hypotension (1.8%), and fatigue (1.6%). The incidence of cough was 0.4%.
Oparil et al.[99] (2009) COACH	DB, factorial, MC, PC, RCT	N=1,940 8 weeks	Primary: Mean change in DBP and SBP at	Primary: Reductions in mean DBP as a result of combination treatment were similar between subgroups. Patients with stage 1 HTN achieved reductions of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Amlodipine 5 to 10 mg QD and olmesartan 10 to 40 mg vs amlodipine 5 to 10 mg QD vs olmesartan 10 to 40 mg QD vs placebo	Patients ≥18 years of age with seated DBP 95 to 120 mm Hg, with a subgroup analysis based on HTN (stage 1: SBP 140 to 159 mm Hg or DBP 90 to 99 mm Hg; stage 2: SBP ≥160 mm Hg or DBP ≥100 mm Hg) and no prior antihypertensive medication		week 8 for each subgroup Secondary: Proportion of patients achieving blood pressure goal (<140/90 mm Hg or <130/80 mm Hg)	14.8 to 15.8 mm Hg and patients with stage 2 HTN achieved reductions of 13.6 to 19.8 mm Hg. Reductions in mean SBP as a result of combination treatment resulted in greater reductions in patients with stage 2 HTN (25.1 to 32.7 mm Hg) compared to stage 1 HTN (17.7 to 23.7 mm Hg) (P value not reported). Reductions in mean DBP and SBP were similar between those with no prior antihypertensive treatment and those with prior hypertensive treatment. Secondary: The proportion of patients with stage 1 HTN who received combination treatment and achieved blood pressure goal was 65.6 to 80.0%, compared to 40.5 to 66.7% of those who received monotherapy (P<0.0001 across treatments). The proportion of patients with stage 2 HTN who received combination treatment and achieved BP goal was 40.5 to 49.2%, compared to 13.1 to 29.2% of those who received monotherapy (P<0.0001). Results of patients with baseline SBP ≥180 mm Hg were similar to other subgroups.
Braun et al.[100] (abstract) (2009) Amlodipine 10 mg plus olmesartan 20 mg QD If patients were uncontrolled after 4 weeks, they were changed to amlodipine and valsartan 10-160 mg QD.	OL, PRO Patients with DBP 100 to 109 mm Hg	N=257 8 weeks	Primary: Reduction in SBP and DBP Secondary: Adverse events	Primary: Following treatment with amlodipine and olmesartan, SBP/DBP decreased by 19.2±12.4/14.4±7.4 mm Hg. The number of patients who progressed to treatment with amlodipine and valsartan was 175. Additional reductions in SBP of 7.9 mm Hg and DBP of 3.9 mm Hg were seen (P<0.0001 for both). Secondary: Both treatments were well tolerated and reported adverse events were consistent with drug profiles.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Elliott et al.[101] (2015) Amlodipine 10 mg QD vs perindopril 16 mg QD vs perindopril + amlodipine 14-10 mg QD	PRO, RCT Hypertensive patients 18 to 75 years of age	N=820 42 days	Primary: Change in mean seated office trough DBP from baseline to day 42 Secondary: Mean seated office SBP, responder rates (those achieving target BP of (<140/90 for non–diabetics, <130/80 for diabetics) , safety	Primary: Least square mean BP changes over the 42 days of treatment: −12.7/−9.1 mmHg for perindopril, −18.8/−12.9 mmHg for amlodipine, and −22.8/−15.4 mmHg for the combination of perindopril + amlodipine. Changes in both office systolic and diastolic BPs were significantly greater with combination therapy, at 42 days of therapy (−10.1/−6.3 mmHg vs perindopril, both P<0.0001, and −3.9/2.5 mmHg vs amlodipine, both P<0.002). Analogous analyses restricted to the per–protocol population provided similar results. Secondary: Regardless of the duration of therapy, or the intent–to–treat or "per protocol" population, a significantly greater proportion of subjects achieved "target BP" in the perindopril + amlodipine group, compared with perindopril or amlodipine alone: in the pre–specified analysis, the proportions were 52.4% versus 37.1% versus 25.9%, respectively (P<0.0001). The combination showed a lower incidence of pedal edema and adverse events compared with amlodipine. No deaths or significant differences across groups in early discontinuation, serum potassium, or rates of total or serious adverse events or glomerular filtration, were observed.
Manolis et al.[102] (2015) Fixed-dose combination perindopril-amlodipine (available in dosages of 5/5, 5/10, 10/5, or 10/10 mg)	OBS, PRO Ambulatory men or women ≥18 years of age with diagnosed essential hypertension that was treated with daily fixed-dose combination perindopril arginine-amlodipine	N=2,231 6 months	Primary: BP reduction over six months Secondary: BP control after six months	Primary: SBP and DBP of patients who received perindopril-amlodipine decreased significantly versus baseline after three months and six months in the per protocol set (P<0.001). Mean systolic BP decreased from 157.0±15.4 mmHg to 129.0±7.9 mmHg after six months, and diastolic BP from 91.5±10.1 to 78.8±6.7 mmHg (both P<0.001). Secondary: BP control (<140/90 mmHg) was achieved in 84.8% of the per protocol set.
Littlejohn et al.[103] (2009)	DB, MC, PC, RCT Patients ≥18 years	N=2,607 8 weeks	Primary: Change in the in-clinic seated	Primary: Both telmisartan (irrespective of amlodipine dosage; P<0.0001) and amlodipine (irrespective of telmisartan dosage; P<0.0001) significantly

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Amlodipine 2.5 to 10 mg QD and telmisartan 20 to 80 mg QD vs telmisartan 20 to 80 mg QD vs amlodipine 2.5 to 10 mg QD vs placebo	of age with Stage 1 or 2 HTN (DBP ≥95 and ≤119 mm Hg)		diastolic BP Secondary: Change in the in-clinic seated SBP, DBP and SBP response (DBP <90 mm Hg, decrease in DBP ≥10 mm Hg, SBP <140 mm Hg, decrease in SBP ≥15 mm Hg), and BP control (DBP <90 mm Hg and SBP <140 mm Hg)	lowered the in-clinic DBP. The greatest reduction in blood pressure was with telmisartan 80 mg plus amlodipine 10 mg (SBP/DBP -26.4/-20.1 mm Hg; P<0.05 vs both monotherapies). DBP and SBP response was achieved by 91.2 and 90.4% of patients in the telmisartan 80 mg plus amlodipine 10 mg group, respectively. More than 50% of patients treated with combination therapy achieved blood pressure control, with the highest percentages (76.5% [overall control] and 85.3% [DBP control]) being achieved by patients treated with telmisartan 80 mg plus amlodipine 10 mg. A total of 37.3% of patients reported at least one adverse event. The most commonly reported adverse events were headache (5.4%) and peripheral edema (4.4%). Headache was more frequent in the placebo group (10.9%) compared to the telmisartan monotherapy (5.9%), amlodipine monotherapy (6.0%), and combination therapy (4.7%). The incidence of peripheral edema was highest in the amlodipine 10 mg group (17.8%); however, this rate was lower when amlodipine was used in combination with telmisartan: 11.4% (telmisartan 20 mg and amlodipine 10 mg), 6.2% (telmisartan 40 mg and amlodipine 10 mg), and 11.3% (telmisartan 80 mg and amlodipine 10 mg).
Littlejohn et al.[104] (2009) Telmisartan and amlodipine 40-5 mg QD (fixed-dose combination product) vs telmisartan and amlodipine 40-10	DB, DD, MC, PC, PG, RCT Patients ≥18 years of age with stage 1 or 2 HTN (DBP ≥95 and ≤119 mm Hg), with a subgroup analysis including patients with DBP ≥100 mm Hg at baseline	N=1,078 8 weeks	Primary: Change in DBP from baseline to study end point Secondary: Change from baseline to study end in SBP; percent of patients achieving a DBP response (DBP <90 mm Hg) and SBP	Primary: Significant reductions in DBP were seen from baseline to study end for both dual therapy and monotherapy (P values not reported). Amlodipine 5 and 10 mg with telmisartan 40 and 80 mg significantly reduced DBP compared to respective monotherapies (P values not reported). Secondary: Amlodipine 5 and 10 mg with telmisartan 40 and 80 mg significantly reduced SBP compared to respective monotherapies (P values not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg QD (fixed-dose combination product) vs telmisartan and amlodipine 80-5 mg QD (fixed-dose combination product) vs telmisartan and amlodipine 80-10 mg QD (fixed-dose combination product) vs respective monotherapies, dosing frequency not specified			response (SBP <140 mm Hg or reduction from baseline ≥15 mm Hg); percent of patients achieving BP control (SBP/DBP <140/<90 mm Hg) and DBP control (<90 mm Hg) and safety	Combination therapy resulted in a greater DBP and SBP response than monotherapy (P values not reported). The highest rate of BP control was achieved with amlodipine 10 mg with telmisartan 80 mg. Rates of adverse events were similar between dual therapy and monotherapy. Incidences of adverse events were 4.40% with telmisartan monotherapy, 11.00% with amlodipine monotherapy and 11.75% with combination therapy. The most commonly reported events were headache and peripheral edema. Patients receiving amlodipine 10 mg had the highest incidence of peripheral edema; however rates were lower when amlodipine was used in combination with telmisartan.
Sharma et al.[105] (2007) Telmisartan and amlodipine 40-5 mg QD (fixed-dose combination) vs	DB, MC, RCT Patients 18 to 65 years of age with established stage 2 uncomplicated essential HTN	N=210 12 weeks	Primary: SBP/DBP reductions and responder rates (SBP/DBP <130/<80 mm Hg) Secondary: Not reported	Primary: There was a significant reduction from baseline in mean SBP in both groups (telmisartan and amlodipine, from 176.3 to 128.0 mm Hg; amlodipine, from 171.8 to 143.4 mm Hg; both, P<0.05 vs baseline). There was a significant reduction in SBP from baseline in the telmisartan and amlodipine and amlodipine groups (-27.4 and -16.6%, respectively; P<0.05 within group and between groups). There was a significant reduction from baseline in mean DBP in both treatment groups (telmisartan and amlodipine, from 100.9 to 93.8 mm Hg;

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amlodipine 5 mg QD				amlodipine, from 99.7 to 94.3 mm Hg; both, P<0.05). There was a 20.2% reduction in mean DBP in the telmisartan and amlodipine group, which was significantly greater compared to the reduction of 12.7% observed in the amlodipine group (P<0.05 between groups and within both groups). A total of 87.3% of patients receiving telmisartan and amlodipine reached the target SBP/DBP goal, compared to 69.3% of patients receiving amlodipine (P<0.05). A total of 16.0% of patients in the telmisartan and amlodipine group experienced adverse events compared to 15.4% of patients in the amlodipine group (P value not significant). The most common adverse events in the telmisartan and amlodipine group were peripheral edema (8.5%), headache (5.7%), dizziness and cough (3.8%), and diarrhea (1.9%). Secondary: Not reported
Neutel et al.[106] (2012) TEAMSTA Telmisartan and amlodipine 80-10 mg QD (fixed-dose combination product) vs telmisartan 80 mg QD vs amlodipine 10 mg QD	DB, MC, PG, RCT Patients ≥18 years of age with severe HTN	N=858 8 weeks	Primary: Change in baseline blood pressure, blood pressure goal and response rates Secondary: Safety	Primary: Reductions in seated trough cuff blood pressure (-47.5/-18.7 mm Hg) were significantly greater with combination therapy compared to telmisartan (P<0.001) or amlodipine (P=0.002). Significant reductions with combination therapy were observed at one, two, four, and six weeks. Blood pressure goal and response rates were consistently higher with combination therapy (50.4 and 91.4 to 99.7%) compared to monotherapy with either agent (24.1 and 69.3 to 91.5% and 35.6 and 83.9 to 98.5%). Secondary: Combination therapy was well tolerated and fewer adverse events were reported with combination therapy compared to amlodipine (12.6 vs 16.4%). Peripheral edema was reported more frequently with amlodipine compared to combination therapy (13.2 vs 9.3%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Maciejewski et al.[107] (2006) Amlodipine 5 to 10 mg QD vs valsartan 80 to 160 mg QD If blood pressure exceeded 140/90 while on highest treatment dose, HCTZ 12.5mg/day was added to the regimen.	DB, PRO, RCT, XO African-Americans, older than 35 years, with baseline blood pressure >140/90 mm Hg and not on antihypertensive treatment	N=20 8 to 10 weeks for each arm with 2 week washout period before crossover	Primary: Comparison of 24-hr ABPM recordings Secondary: Magnitude of change from baseline in SBP and DBP with each treatment, percent of patients who achieved goal <140/<90 with each treatment based on clinic blood pressure measurements	Primary: There was no difference between the groups based on 24-hr ABPM: SBP amlodipine 130±8 vs valsartan 127±17 (P=0.350) and DBP amlodipine 82±5 vs valsartan 84±16 (P=0.430). Secondary: There was no difference between groups in magnitude of change from baseline in blood pressure (amlodipine -25±8/-18±7 vs valsartan -25±9/-16±7; P=0.61), and in percent of patients achieving goal blood pressure, 70% in the valsartan group and 75% in the amlodipine group (P=0.62).
Ichihara et al.[108] (2006) Amlodipine 2.5 to 10 mg QD vs valsartan 40 to 160 mg QD	RCT Patients with untreated HTN (clinic SBP >140 mm Hg and/or DBP >90 mm Hg; or ABPM SBP >135 mm Hg and/or DBP >98 mm Hg)	N=100 12 months	Primary: ABPM and clinic blood pressure Secondary: Pulse wave velocity, carotid intima-media thickness, urinary albumin excretion	Primary: Both treatments resulted in significant decreases in blood pressure, both ambulatory and clinic, over 12 months from baseline; blood pressure decreases were similar between treatment groups (between treatments: clinic SBP P=0.34; clinic DBP P=0.85; 24 hour ABPM P=0.14). Blood pressure variability decreased significantly in the amlodipine group compared to the valsartan group, where there was no change in blood pressure variability (P<0.01). Secondary: The decrease in pulse wave velocity was significant from baseline for both groups, but not significantly different from each other (P<0.05 from baseline). Intima-media thickness was not changed significantly from baseline for either treatment (P>0.05 for both from baseline). Urinary albumin excretion in the valsartan group decreased significantly

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				both from baseline and compared to amlodipine treatment (P<0.05 from baseline, P value for comparison not reported).
Karpov et al.[109] (2012) Amlodipine and valsartan 5-80, 5-160, 10-160 mg QD (fixed-dose combination product)	OL, OS, PRO Patients with HTN	N=8,336 3 months	Primary: Baseline reductions in blood pressure, blood pressure control (<140/90 mm Hg) Secondary: Safety	Primary: Reductions in blood pressure were dose related. Overall, mean reductions in blood pressure ranged from 165.0/99.3 mm Hg at baseline to 128.7/80.4 mm Hg at 12 weeks (-36.3/-18.9 mm Hg; P<0.0001). A total of 77.7% of patients achieved blood pressure control. Secondary: A total of 5.3% of patients reported adverse events. The incidence of edema declined from 10.4% at baseline to 8.5% at trial end.
Philipp et al.[110] (2007) <u>Study 1</u> Amlodipine 2.5 to 5 mg and valsartan 40 to 320 mg QD vs amlodipine 2.5 to 5 mg QD vs valsartan 40 to 320 mg QD vs placebo	DB, MC, PC, RCT Males and females, ages 18 years and older with HTN (mean sitting DBP ≥95 mm Hg and <110 mm Hg)	N=1,911 8 weeks	Primary: Mean sitting DBP Secondary: Change in mean sitting SBP, response rate (proportion of patients with mean sitting DBP <90 mm Hg or a ≥10 mm Hg reduction from baseline), control rate (proportion of patients with mean sitting DBP <90 mm Hg), adverse events (combined with study 2)	Primary: All treatments significantly decreased mean sitting DBP from baseline (P<0.05). Combination treatment resulted in significantly greater blood pressure reduction than either monotherapy (P<0.05 for all combinations compared to respective doses of monotherapy except amlodipine 2.5 mg and valsartan 40 mg QD). Secondary: All treatments significantly decreased mean sitting SBP from baseline (P<0.05). Combination treatment resulted in significantly greater blood pressure reduction than either monotherapy (P<0.05 for all combinations compared to respective doses of monotherapy). Response rates were significantly different from placebo for all treatment groups (P<0.05). Response rates for combination products were significantly different than each monotherapy for the following combinations: amlodipine 5 mg plus valsartan 80 mg, amlodipine 5 mg plus valsartan 40 mg and amlodipine 2.5 mg plus valsartan 80 mg (P<0.05 for each combination compared to both monotherapy).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Response rates for all combinations produced significantly improved compared to either one of the monotherapies except amlodipine 2.5 mg plus valsartan 40 mg (P<0.05 for each combination compared to one of the respective monotherapy). Control rates with therapy were significantly better than placebo, with the highest control rate achieved with amlodipine 5 mg plus valsartan 320 mg (P<0.05 compared to placebo, P value not reported for others). Adverse event rates were not significantly different among combination treatment, amlodipine treatment, and placebo. Adverse event rates were significantly different between amlodipine plus valsartan and valsartan monotherapy (P<0.05). The most commonly reported adverse events for combination treatment were: peripheral edema, headache, nasopharyngitis, upper respiratory tract infection and dizziness. Peripheral edema occurred significantly less frequently in the combination treatment group than the amlodipine monotherapy group (5.4 vs 8.7%; P=0.014) and significantly more frequently than in the valsartan monotherapy group (5.4 vs 2.1%; P<0.001). Peripheral edema occurrence in the valsartan group was similar to the rate in the placebo group.
Philipp et al.[111] (2007) <u>Study 2</u> Amlodipine 10 mg and valsartan 160 or 320 mg QD vs amlodipine 10 mg QD	DB, MC, PC, RCT Male and females, ages 18 years and older with hypertension (mean sitting DBP ≥95 mm Hg and <110 mm Hg)	N=1,250 8 weeks	Primary: Mean sitting DBP Secondary: Change in mean sitting SBP, response rate (proportion of patients with mean sitting DBP <90 mm Hg or a ≥10 mm Hg reduction from baseline),	Primary: Mean sitting DBP was significantly reduced for both combination as compared to the individual components and to placebo (P<0.05). Secondary: Response rates and control rates for combination treatments were significantly greater than valsartan monotherapy therapy and placebo therapy, but not different from amlodipine monotherapy (P<0.05). Adverse event rates were not significantly different between combination treatment, amlodipine treatment and placebo. Adverse event rates were significantly different between amlodipine plus

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vs valsartan 160 to 320 mg QD vs placebo			control rate (proportion of patients with mean sitting DBP <90 mm Hg), adverse events (combined with study 1)	valsartan and valsartan monotherapy (P<0.05).
Philipp et al.[112] (abstract) (2011) Amlodipine and valsartan 10-160 or 10-320 mg/day (fixed-dose combination product) vs amlodipine 10 mg/day vs valsartan 160 or 320 mg/day vs placebo	Post-hoc analysis Patients with HTN	N=834 Not reported	Primary: Rate of blood pressure control (<140/90 mm Hg), change in baseline blood pressure Secondary: Safety	Primary: Two weeks after starting therapy, blood pressure control rates were greater with amlodipine and valsartan 10-320 mg/day (49%) vs monotherapies (32 to 38%) and placebo (16%). Consistent results were observed in patients with stage 1 and 2 HTN. Among patients receiving combination therapy, statistically significant differences were observed at endpoint vs comparators. At all baseline blood pressure levels, the probability of achieving a blood pressure <140/90 or <130/80 mm Hg was greater with combination therapy compared to monotherapies and placebo. Secondary: Overall adverse events incidence was similar with combination therapy vs monotherapies and placebo.
Schunkert et al.[113] (2009) Amlodipine and valsartan 10-160 mg	RCT, MC, DB, AC Patients ≥18 years of age with mild to moderate essential	N=944 8 weeks	Primary: Change from baseline in mean sitting DBP	Primary: At week eighth, a significantly greater reduction from baseline in msDBP was observed with amlodipine and valsartan (11.4 mm Hg) compared to amlodipine monotherapy (9.3 mm Hg; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD (fixed-dose combination product) vs amlodipine 10 mg QD	HTN (mean sitting DBP ≥90 mm Hg and <110 mm Hg) who were inadequately controlled on amlodipine 10 mg		Secondary: Change from baseline in mean sitting SBP, responder rate (mean sitting DBP <90 mm Hg or ≥10 mm Hg reduction from baseline) and DBP control rate (mean sitting DBP <90 mm Hg)	Secondary: At week eight, a significantly greater reduction from baseline in msSBP was observed with amlodipine and valsartan (12.9 mm Hg) compared to amlodipine monotherapy (10.0 mm Hg; P<0.0001). The mean reductions in mean sitting SBP/mean sitting DBP were 24.4/17.2 and 21.6/15.0 mm Hg for the amlodipine and valsartan and amlodipine monotherapy, respectively The responder rate was significantly greater with amlodipine and valsartan (79.0%) than with amlodipine monotherapy (70.1%; P=0.0011). The percentage of patients with controlled DBP was significantly higher with amlodipine and valsartan (77.8%) compared to amlodipine monotherapy (66.5%; P<0.0001). The incidence of peripheral edema was higher with amlodipine monotherapy (9.4%) compared to amlodipine and valsartan (7.6%).
Ke et al.[114] (2010) Amlodipine and valsartan 5-80 mg QD (fixed-dose combination) vs amlodipine 5 mg QD	AC, DB, MC, RCT Hypertensive patients 18 to 86 years of age with mean sitting DBP ≥95 and <110 mm Hg who were inadequately controlled on amlodipine 5 mg for 4 weeks	N=698 8 weeks	Primary: Change in mean sitting DBP Secondary: Change in mean sitting SBP, diastolic response rate (mean sitting DBP <90 mm Hg or ≥10 mm Hg decrease from baseline), diastolic control rate (mean sitting DBP <90 mmHg) and overall BP control rate (mean sitting SBP/DBP	Primary: At week eight, the reduction in mean sitting DBP was greater with amlodipine and valsartan (11.4/9.7 mm Hg) compared to amlodipine (7.4/7.1 mm Hg; P<0.0001). Secondary: At week eight, the diastolic control and response rates were significantly greater in the amlodipine and valsartan compared to amlodipine monotherapy (diastolic control, 75.5 vs. 64.5%; P=0.0002 and response rates, 79.3 vs. 66.8% [P<0.0001], respectively). The proportion of patients achieving overall blood pressure control was greater in the amlodipine and valsartan group compared to amlodipine monotherapy (69.2 vs. 57.6%, P=0.0013). More than 50% of patients not adequately controlled on amlodipine monotherapy achieved blood pressure control after two weeks of therapy with amlodipine and valsartan. In a subgroup of patients, there was a significant reduction in 24-hr mean blood pressure from baseline with amlodipine and valsartan (-7.3/-6.3 mm

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			<140/90 mmHg)	Hg; P<0.0001). There was no significant difference with amlodipine from baseline (-0.2/+0.3 mm Hg; P>0.05).
Destro et al.[115] (2008) Ex-EFFeCTS Amlodipine and valsartan 5-160 mg QD for 2 weeks, followed by 10-160 mg QD for 6 weeks (fixed-dose combination product) vs amlodipine 5 mg QD for 2 weeks, followed by 10 mg QD for 6 weeks HCTZ 12.5 mg could be added at week 4 if mean sitting SBP was ≥130 mm Hg.	DB, MC, RCT Patients ≥18 years of age with stage 2 HTN (mean sitting SBP ≥160 mm Hg)	N=646 8 weeks	Primary: Mean changes in mean sitting SBP at week 4 Secondary: Change from baseline in mean sitting DBP at week 4; change in mean sitting blood pressure at weeks 2, 4, and 8; overall blood pressure control rate at week 8 (mean sitting SBP/DBP <140/90 mm Hg)	Primary: At week four, reductions in mean sitting SBP were significantly greater in patients receiving amlodipine and valsartan (30.1 mm Hg) than in those receiving amlodipine (23.5 mm Hg; P<0.0001). At week four, mean sitting SBP reductions in patients with baseline mean sitting SBP ≥180 mm Hg were greater for amlodipine and valsartan (40.1 mm Hg) than for those receiving amlodipine (-31.7 mm Hg; P=0.0018). Secondary: At week four, reductions in mean sitting DBP were significantly greater in patients receiving amlodipine and valsartan (12.5 mm Hg) than in those receiving amlodipine (8.6 mm Hg; P<0.0001) and all other time points (data not provided). At week four, 45.3% of patients were controlled on amlodipine and valsartan compared to 23.8% on amlodipine monotherapy. At week eight, corresponding control rates were 53.0 and 31.1%, respectively (P<0.0001).
Flack et al.[116] (2009) EX-STAND Amlodipine and valsartan 5-160 mg QD for 2 weeks, followed by 10-160 mg QD for 10 weeks	AC, DB, MC, RCT African American patients ≥18 years of age with stage 2 HTN (mean sitting SBP ≥160 and <200 mm Hg)	N=572 12 weeks	Primary: Change in mean sitting SBP from baseline to week 8 Secondary: Change in mean sitting SBP from baseline to week 8; change from	Primary: At week eight, treatment with amlodipine and valsartan significantly decreased mean sitting SBP (33.3 mm Hg) compared to amlodipine monotherapy (26.6 mm Hg; P<0.0001). Secondary: Amlodipine and valsartan produced significantly greater reductions in mean sitting DBP from baseline compared to amlodipine monotherapy throughout the study: week two (9.7 vs 6.9 mm Hg; P=0.0001), week four (13.2 vs 10.7 mm Hg; P=0.0008), week eight (14.0 vs 11.2 mm Hg;

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vs amlodipine 5 mg QD for 2 weeks, then 10 mg QD for 10 weeks If SBP was ≥130 mm Hg at week 4, amlodipine and valsartan could be titrated to 10-320 mg dose. At week 8, HCTZ 12.5 mg was optionally added to both amlodipine and valsartan and amlodipine if SBP ≥130 mm Hg.			baseline in mean sitting SBP and DBP after 2, 4, 8 and 12 weeks of treatment; blood pressure control (<140/90mmHg) after 12 weeks of therapy	P=0.0002), and week 12 (16.1 vs 12.8 mm Hg; P<0.0001). At week eight, 49.8% of patients in the amlodipine and valsartan group and 30.2% in the amlodipine monotherapy group had their blood pressure controlled to <140/90 mm Hg (OR, 2.4; P<0.0001). At week 12, 57.2% of patients in the amlodipine and valsartan group and 35.9% in the amlodipine monotherapy group attained blood pressure <140/ 90 mm Hg (OR, 2.5; P<0.0001).
Schrader et al.[117] (2009) Amlodipine and valsartan 5-160 mg QD for 12 weeks (fixed-dose combination product) vs amlodipine 10 mg QD for 8 weeks, followed by amlodipine and valsartan 5-160 mg QD for 4 weeks	DB, MC, RCT Hypertensive patients who were ≥55 years of age with mean sitting SBP ≥130 and ≤160 mm Hg who were inadequately controlled on amlodipine 5 mg for 4 weeks	N=1,183 12 weeks	Primary: Change in mean sitting systolic SBP Secondary: Change in mean sitting SBP and DBP, SBP control rate (mean sitting SBP <130 mm Hg), overall blood pressure control rate (blood pressure <140/90 mm Hg for nondiabetic patients and <130/80 mm Hg	Primary: At week eight, there was a greater reduction in mean sitting SBP with amlodipine and valsartan (-8.01 mm Hg) than with amlodipine (-5.95 mm Hg; P<0.001 for non-inferiority and P=0.002 for superiority). Secondary: Non-inferiority was also observed at week four (-8.29 vs -6.29; P<0.001) and week eight (-8.23 vs -6.13; P<0.001) in mean sitting SBP, at week 4 (-5.02 vs -4.23; P<0.001) and week eight (-4.70 vs -4.06; P<0.001) in mean sitting DBP, and at week 12 after the switch from amlodipine to amlodipine and valsartan (-9.13 vs -8.16; P<0.001 for mean sitting SBP and -5.52 vs -4.90; P<0.001 for mean sitting DBP). Systolic control with amlodipine and valsartan was greater than with amlodipine at week four (34.98 vs 24.83%; P<0.001) and week eight (34.28 vs 26.21%; P=0.019), and similar after the switch from amlodipine 10 mg to amlodipine and valsartan at week 12 (38.04 vs 31.81%; P=0.162).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(fixed-dose combination product)			for diabetic patients), and SBP response (mean sitting SBP <130 mm Hg or ≥20 mm Hg reduction from baseline)	SBP response rates were higher with amlodipine and valsartan than with amlodipine at week four (37.20 vs 26.72%, P<0.001) and week eight [36.57 vs 27.77%; P=0.009), and similar after the switch from amlodipine to amlodipine and valsartan at week 12 (40.36 vs 35.76%; P=0.347). The incidence of peripheral edema was significantly lower with amlodipine and valsartan than with amlodipine (6.6 vs 31.1%, P<0.001). Peripheral edema resolved in 56% patients who switched from amlodipine and valsartan without the loss of effect on blood pressure reduction.
Sinkiewicz et al.[118] (2009) Amlodipine and valsartan 10-160 mg or 5-160 mg QD (fixed-dose combination product) vs valsartan 160 mg QD	AC, DB, MC, RCT Patients ≥18 years of age with essential HTN (mean sitting DBP ≥90 mm Hg and <110 mm Hg) who were inadequately controlled on valsartan 160 mg	N=947 8 weeks	Primary: Change from baseline in mean DBP Secondary: Change from baseline in mean sitting SBP, responder rate (mean DBP <90 mm Hg or ≥10 mm Hg reduction from baseline), and DBP control rate (mean DBP < 90 mm Hg)	Primary: At week eight, a significantly greater reduction in mean DBP was observed with both amlodipine and valsartan combinations (10-160 mg: -11.5 mm Hg, 5-160 mg: -9.6 mm Hg; P<0.0001 for both) compared to valsartan monotherapy (-6.7 mm Hg). Secondary: At week eight, a significantly greater reduction in mean SBP was observed in both amlodipine and valsartan combinations (10-160 mg: -14.3 mm Hg, 5-160 mg: -12.2 mm Hg; P<0.0001 for both) compared to valsartan monotherapy (-8.3 mm Hg). Overall mean SBP/DBP reductions of 22.5/15.5 and 21.3/13.7 mm Hg were observed in the amlodipine and valsartan 10-160 and 5-160 mg treatment groups, respectively compared to 16.7/11.4 mm Hg in the valsartan 160 mg group. The amlodipine and valsartan 10-160 mg combination showed a significantly greater reduction in mean SBP/DBP compared to amlodipine and valsartan 5-160 mg (P<0.001). Responder rates were higher in both amlodipine and valsartan groups (10-160 mg: 81% [P<0.0001]; 5-160 mg: 68% [P=0.0018], respectively) compared to valsartan monotherapy (57%). Peripheral edema was the most frequent adverse event, which was reported in 9.1% of patients receiving amlodipine and valsartan (10-160 mg), 0.9% of patients receiving amlodipine and valsartan (5-160 mg), and

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				1.3% of patients receiving valsartan monotherapy.
Fogari et al.[119] (2009) Amlodipine and valsartan 5 to 10-160 mg/day (fixed-dose combination) vs irbesartan and HCTZ 300-12.5 to 25 mg/day (fixed-dose combination product)	Blind end endpoint, OL, PG, PRO, RCT Patients 75 to 89 years of age with moderate essential HTN (SBP ≥160, DBP >95 to <110 mm Hg)	N=94 24 weeks	Primary: Proportion of patients achieving DBP <90 mm Hg Secondary: Changes in ambulatory blood pressure, lying and standing changes in blood pressure, safety	Primary: The proportion of patients receiving valsartan and amlodipine and irbesartan and HCTZ who achieved blood pressure <140/<90 mm Hg was 82.9 and 85.1% (P value not significant between groups). Secondary: Both treatment combinations resulted in a significant decrease in ambulatory blood pressure without any differences between treatment groups (P<0.001 from baseline, P>0.05 between groups). Results were similar between groups for lying SBP/DBP but patients receiving irbesartan and HCTZ experienced greater changes in ambulatory blood pressure than those receiving valsartan and amlodipine (17.2/9.0 vs 10.1/1.9 mm Hg; P<0.05 for SBP and P<0.01 for DBP). Changes from baseline in serum potassium (decrease) and uric acid (increase) were significant for those receiving irbesartan and HCTZ, but not valsartan and amlodipine (P<0.05 for irbesartan and HCTZ).
Poldermans et al.[120] (2007) Amlodipine 5 to 10 mg QD and valsartan 160 mg QD vs lisinopril 10 to 20 mg and HCTZ 12.5 mg QD	AC, DB, MC, PG, RCT Males and females, ages 18 years and older with HTN (mean DBP ≥110 mm Hg and <120 mm Hg)	N=130 6 weeks	Primary: Safety/adverse events, vital signs, hematology, biochemistry variables Secondary: Efficacy (mean DBP, response rate, proportion of patients with mean DBP <90 mm Hg or a ≥10 mm Hg reduction from baseline)	Primary: Both treatments were well tolerated, 26 (40.6%) of patients receiving amlodipine and valsartan and 21 (31.8%) of patients receiving lisinopril and HCTZ reported an adverse events and most were not considered drug related. Peripheral edema was reported more often in the amlodipine and valsartan group than the lisinopril and HCTZ group (7.7 vs 1.5%) and cough was reported less often in the amlodipine and valsartan group than the receiving lisinopril and hydrochlorothiazide group (1.6 vs 3.0%). No difference was found between the treatments in changes in laboratory values or biochemistry variables. Secondary: Both treatments led to a reduction in mean SBP and DBP (P<0.0001 for both from baseline) but were not significantly different from each other. Mean blood pressure for each group at study end: amlodipine and

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				valsartan 135.0/83.6 mm Hg and lisinopril and HCTZ 138.7/85.2 mm Hg. The response rate was similar among the groups (100 vs 95.5%; P value not significant).
Calhoun et al.[121] (2009) Amlodipine and valsartan and HCTZ 10-320-25 mg QD (fixed-dose combination product) vs valsartan and HCTZ 320-25 mg QD (fixed-dose combination product) vs amlodipine and valsartan 10-320 mg QD (fixed-dose combination product) vs amlodipine and HCTZ 10-25 mg QD (fixed-dose combination product)	DB, MC, RCT Patients 18 to 85 years of age with moderate to severe essential HTN	N=2,271 8 weeks	Primary: Difference in mean sitting diastolic blood pressure and mean sitting systolic blood pressure Secondary: Not reported	Primary: At each assessment after week three, a significantly greater proportion of patients receiving triple therapy achieved overall blood pressure control (<140/90 mm Hg) compared to those receiving any of the dual therapies (P<0.0001 for all). At end point, 70.8% of patients in the triple therapy group achieved control, compared to 48.3% for valsartan and HCTZ, 54.1% for amlodipine and valsartan, and 44.8% for amlodipine and HCTZ (P<0.0001 for all). Triple therapy improved blood pressure control significantly better than any of the dual therapies. Secondary: Not reported

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Calhoun et al.[122] (2009) Amlodipine and valsartan and HCTZ 10-320-25 mg QD (fixed-dose combination product) vs valsartan and HCTZ 320-25 mg QD (fixed-dose combination product) vs amlodipine and valsartan 10-320 mg QD (fixed-dose combination product) vs amlodipine and HCTZ 10-25 mg QD (fixed-dose combination product)	Secondary analysis Patients 18 to 85 years of age with moderate to severe HTN (mean SBP/DBP ≥145/≥100 mm Hg)	N=2,271 8 weeks	Primary: Proportion and mean SBP of patients with mean SBP reductions ≥60, ≥50, ≥40, ≥30 and ≥20 mm Hg at week three and at the end of the study Secondary: Changes from baseline in mean SBP based upon baseline severity, SBP control rates, safety	Primary: The proportion of patients with mean SBP reductions ≥20 mm Hg was greater with triple therapy than dual therapy at week three (74.5 vs 58.8 to 65.5%) and at study endpoint (87.6 vs 75.8 to 81.5%). More patients who received triple therapy, as compared to dual therapy, achieved mean SBP reductions of ≥30, ≥40, ≥50 and ≥60 mm Hg at week three and at study endpoint (P value not reported). In patients with severe SBP (≥180 mm Hg), triple therapy resulted in significantly greater reductions than those for each dual therapy at week three (P<0.01), except for amlodipine/valsartan (P=0.11). Secondary: Patients with higher baseline mean SBP had greater reductions in mean SBP than those with lower baseline mean SBP. Changes in mean SBP were significantly greater for triple therapy than dual therapy for all baseline SBP (P<0.05), except for valsartan and HCTZ and amlodipine and HCTZ in patients with baseline mean SBP 150 to <160 mm Hg (P value not reported). Significantly more patients (91.8%) receiving triple therapy achieved SBP control (≥20 mm Hg reduction or mean SBP <140 mm Hg) compared to those receiving amlodipine and HCTZ (80.1%), valsartan and HCTZ (80.8%) or valsartan and amlodipine (85.7%) (P<0.01 for all). The overall incidence of adverse events was comparable across treatments, regardless of baseline blood pressure severity.
Pareek et al.[123] (2010) Amlodipine 2.5 to 5	AC, MC, OL, RCT Adults with either untreated or	N=190 12 weeks	Primary: Change in SBP and DBP	Primary: At the end of four weeks, the mean change in SBP (-30.0±10.4 vs -25.08±9.05; P=0.008) and DBP (-18.10± 7.45 vs -14.78±7.48; P=0.021) was significantly greater in the low-dose combination therapy as compared

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mg and atenolol 25 to 50 mg QD vs atenolol 25 to 50 mg QD	pretreated essential HTN		Secondary: Not reported	to the low-dose monotherapy. At the end of 12 weeks, the mean SBP (127.82±8.90 vs 138.0±14.4; P=0.001) and mean DBP (81.73±8.78 vs 87.35±5.50; P=0.011) were significantly lower in the high-dose combination group as compared to the high-dose monotherapy group. Secondary: Not reported
Gustin et al.[124] (1996) Felodipine 5 to 10 mg QD vs nifedipine 30 to 60 mg QD	XO Patients with HTN, stable on nifedipine for ≥3 months were switched to felodipine	N=127 2 months	Primary: Blood pressure Secondary: Side effects and use of supplemental antihypertensive agents	Primary: There was no difference in SBP before and after switching agents. However, there was a difference in DBP, which was slightly lower (-2±2 mm Hg) with felodipine than with nifedipine treatment (P<0.05). Secondary: Reported adverse events by patients and providers did not differ between the agents, with the most commonly reported side effect for both groups being leg swelling/edema. There was no difference in use of supplemental antihypertensive agents and heart rate between treatments (P>0.05 for both).
Karotsis et al.[125] (2006) Felodipine 5 mg QD vs lisinopril 10 mg QD vs chlorthalidone 12.5 mg QD vs	RCT Patients 25 to 79 years of age with uncontrolled HTN (average office blood pressure >140/90 mm Hg for all or >153/85 mm Hg for diabetics or patients <65 years of age, confirmed on 2 office visits ≥1 week apart) after ≥4 weeks of OL monotherapy with	N=211 8 weeks	Primary: Blood pressure Secondary: Not reported	Primary: There was a significant decline in both office and home SBP and DBP during the trial with all treatments. The antihypertensive effect was more pronounced and reached significance when home blood pressure monitoring was used in comparison to office blood pressure without the white-coat effect (P<0.001 for all blood pressure changes). With or without the white-coat effect, blood pressure still declined and the differences were significant (P<0.0001 for all blood pressure changes). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
valsartan 80 mg QD All patients also received diltiazem 240 mg QD.	diltiazem at 240 mg QD			
Manyemba et al.[126] (1997) reserpine 0.25 mg QD plus HCTZ 25 mg QD vs nifedipine SR 20 mg BID plus HCTZ 25 mg QD plus	OL, RCT, XO African American patients aged 21 to 65 years with HTN (blood pressure >140/95 mm Hg) after 4 weeks of daily HCTZ therapy	N=32 10 weeks	Primary: The change in blood pressure from baseline to the end of each 4-week treatment period Secondary: Not reported	Primary: Reserpine reduced SBP by 15.9 mm Hg (95% CI, 8.4 to 23.4) and DBP by 11.1 mm Hg (95% CI, 7.5 to 14.6). Nifedipine SR reduced SBP by 18.9 mm Hg (95% CI, 12.1 to 25.7) and DBP by 9.6 mm Hg (95% CI, 7.2 to 12.0). There was no significant difference between the two groups. Secondary: Not reported
Lindholm et al.[127] (2005) Other antihypertensive therapies (amiloride, amlodipine, bendro-flumethiazide*, captopril, diltiazem, enalapril, felodipine, HCTZ, isradipine, lacidipine, lisinopril, losartan, or verapamil) or placebo vs	MA 13 RCTs evaluating the treatment of primary HTN with a β-blocker as first-line treatment (in ≥50% of all patients in one treatment group) and outcome data for all-cause mortality, cardiovascular morbidity or both	N=105,951 2.1 to 10.0 years	Primary: Stroke, MI, all-cause mortality Secondary: Not reported	Primary: The RR of stroke was 16% higher with β-blocker therapy than for the comparator therapies (RR, 1.16; 95% CI, 1.04 to 1.30; P=0.009). The RR of stroke was the highest with atenolol (26% higher) compared to other non β-blockers (RR, 1.26%; 95% CI, 15 to 38; P<0.0001). The relative risk of MI was 2% higher for β- blocker therapy than for the comparator therapies (RR, 1.02; 95% CI, 0.93 to 1.12), which was not significant (P value not reported). The RR of all-cause mortality was 3% higher for β-blocker therapy than for the comparator therapies (RR, 1.16; 95% CI, 0.99 to 1.08; P=0.14). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
β-blocker therapy (atenolol, metoprolol, oxprenolol*, pindolol, or propranolol)				
Van Bortel et al.[128] (2008) ACE inhibitor, ARB, β-blocker, calcium channel blocker, or placebo vs nebivolol	MA 12 RCTs involving >25 patients with essential HTN where nebivolol 5 mg QD was compared to placebo or other active drugs for >1 month	N=2,653 Duration varied	Primary: Antihypertensive effect and tolerability Secondary: Not reported	Primary: Overall, higher response rates were observed with nebivolol than all other antihypertensive agents combined (OR, 1.41; 95% CI, 1.15 to 1.73; P=0.001) and compared to the ACE inhibitors (OR, 1.92; 1.30 to 2.85; P=0.001), but response rates to nebivolol were similar to β-blockers (OR, 1.29; 95% CI, 0.81 to 2.04; P=0.283), calcium channel blockers (OR, 1.19; 95% CI, 0.83 to 1.70; P=0.350) and losartan (OR, 1.35; 95% CI, 0.84 to 2.15; P=0.212). Overall, a higher percentage of patients obtained normalized BP with nebivolol compared to the other antihypertensive agents combined (OR, 1.35; 95% CI, 1.07 to 1.72; P=0.012). A higher percentage of patient receiving nebivolol obtained normalized BP compared to losartan (OR, 1.98; 95% CI, 1.24 to 3.15; P=0.004) and calcium channel blockers (OR, 1.96; 95% CI, 1.05 to 1.96; P=0.024), but not when compared to other β-blockers (OR, 1.29; 95% CI, 0.81 to 1.65; P=0.473). Overall, the percentage of adverse events was significantly lower with nebivolol compared to the other antihypertensive agents combined (OR, 0.59; 95% CI, 0.48 to 0.72; P<0.001) and similar to placebo (OR, 1.16; 95% CI, 0.76 to 1.67; P=0.482). In comparing nebivolol to the individual treatments, nebivolol had a lower percentage of adverse events compared to losartan (OR, 0.52; 95% CI, 0.30 to 0.89; P=0.016), the other β-blockers (OR, 0.56; 95% CI, 0.36 to 0.85; P=0.007) and calcium channel blockers (OR, 0.49; 95% CI 0.33 to 0.72; P<0.001), but was similar to ACE inhibitors (OR, 0.75; 95% CI 0.52 to 1.08). Secondary: Not reported
Wiysonge et al.[129]	MA	N=91,561	Primary:	Primary:

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(2007) Other antihypertensive therapies (i.e., placebo, diuretics, calcium channel blockers, or renin-angiotensin system inhibitors) vs β-blockers (atenolol, metoprolol, oxprenolol*, or propranolol)	13 RCTs evaluating patients ≥18 years of age with HTN	Duration varied	All-cause mortality Secondary: Stroke, CHD, cardiovascular death, total cardiovascular disease, adverse reactions	There was not a significant difference observed in all-cause mortality between β-blocker therapy and placebo (RR, 0.99; 95% CI, 0.88 to 1.11; P value not reported), diuretics (RR, 1.04; 95% CI, 0.91 to 1.19; P value not reported) or renin-angiotensin system inhibitors (RR, 1.10; 95% CI, 0.98 to 1.24; P value not reported). There was a significantly higher rate in all-cause mortality with β-blocker therapy compared to calcium channel blockers (RR, 1.07; 95% CI, 1.00 to 1.14; P=0.04). Secondary: There was a significant decrease in stroke observed with β-blocker therapy compared to placebo (RR, 0.80; 95% CI, 0.66 to 0.96). Also there was a significant increase in stroke with β-blocker therapy compared to calcium channel blockers (RR, 1.24; 95% CI, 1.11 to 1.40) and renin-angiotensin system inhibitors (RR, 1.30; 95% CI, 1.11 to 1.53), but there was no difference observed compared to diuretics (RR, 1.17; 95% CI, 0.65 to 2.09). CHD risk was not significantly different between β-blocker therapy and placebo (RR, 0.93; 95% CI, 0.81 to 1.07]), diuretics (RR, 1.12; 95% CI, 0.82 to 1.54), calcium channel blockers (RR, 1.05; 95% CI, 0.96 to 1.15) or renin-angiotensin system inhibitors (RR, 0.90; 95% CI, 0.76 to 1.06). The risk of total cardiovascular disease was lower with β-blocker therapy compared to placebo (RR, 0.88; 95% CI, 0.79 to 0.97). The effect of β-blocker therapy on cardiovascular disease was significantly worse than that of calcium channel blockers (RR, 1.18; 95% CI, 1.08 to 1.29), but was not significantly different from that of diuretics (RR, 1.13; 95% CI, 0.99 to 1.28) or renin-angiotensin system inhibitors (RR, 1.00; 95% CI, 0.72 to 1.3). There was a significantly higher rate of discontinuation due to side effects with β-blocker therapy compared to diuretics (RR, 1.86; 95% CI, 1.39 to 2.50) and renin-angiotensin system inhibitors (RR, 1.41; 95% CI, 1.29 to 1.54), but there was no significant difference compared to calcium channel blockers (RR, 1.20; 95% CI, 0.71 to 2.04). Actual side effects were not reported.
Baguet et al.[130]	MA	N=10,818	Primary:	Primary:

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(2007) Antihypertensive drugs (enalapril, ramipril, trandolapril, candesartan, irbesartan, losartan, olmesartan, telmisartan, valsartan, HCTZ, indapamide SR*, atenolol, amlodipine, lercanidipine*, manidipine*, enalapril, ramipril, trandolapril, and aliskiren) Drugs were used as monotherapy, either at a fixed daily dosage or in increasing dosages. Although cicletanine*, furosemide and spironolactone were considered for inclusion, none of the trials relating to these agents satisfied all inclusion criteria.	Patients greater than 18 years of age with mild or moderate essential HTN (SBP 140 to 179 mm Hg and/or DBP 90 to 109 mm Hg)	8 to 12 weeks	Weighted average reductions in SBP and DBP Secondary: Not reported	Data did not reflect outcomes from direct, head-to-head comparative trials or formal comparisons between drugs. Diuretics (-19.2 mm Hg; 95% CI, -20.3 to -18.0), calcium channel blockers (-16.4 mm Hg; 95% CI, -17.0 to -15.8) and ACE inhibitors (-15.6 mm Hg; 95% CI, -17.6 to -13.6) produced the greatest reductions in SBP from baseline (P values not reported). The magnitude of DBP reductions were generally similar among all drug classes; however, the greatest reductions in DBP from baseline were observed with the β-blocker, atenolol (-11.4 mm Hg; 95% CI, -12.0 to -10.9), calcium channel blockers (-11.4 mm Hg; 95% CI, -11.8 to -11.1) and diuretics (-11.1 mm Hg; 95% CI, -11.7 to -10.5) (P values were not reported). The weighted average reduction of SBP and DBP for each drug class were as follows: Diuretics: -19.2 (95% CI, -20.3 to -18.0) and -11.1 mm Hg (95% CI, -11.7 to -10.5), respectively. β-blockers: -14.8 (95% CI, -15.9 to -13.7) and -11.4 mm Hg (95% CI, -12.0 to -10.9), respectively. Calcium channel blockers: -16.4 (95% CI, -17.0 to -15.8) and -11.4 mm Hg (95% CI, -11.8 to -11.1), respectively. ACE inhibitors: -15.6 (95% CI, -17.6 to -13.6) and -10.8 mm Hg (95% CI, -11.9 to -9.7), respectively. ARBs: -13.2 (95% CI, -13.6 to -12.9) and -10.3 mm Hg (95% CI, -10.5 to -10.1), respectively. Renin inhibitor: -13.5 (95% CI, -14.2 to -12.9) and -11.3 mm Hg (95% CI, -11.7 to -10.9), respectively. Secondary: Not reported
Laurent et al.[131] (2018)	MA	N=5,496	Primary: Change in SBP and	Primary: <u>Perindopril/amlodipine versus perindopril</u>

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Perindopril 3.5 mg/amlodipine 2.5 mg vs RAS-inhibitor monotherapy (perindopril 5 mg, irbesartan 150 mg, or valsartan 80 mg)	Patients >18 years of age with essential HTN (SBP ≥140 mm Hg and/or DBP ≥90 mm Hg) with an SBP assessment at baseline and at month one	two to nine months	DBP from baseline after one month of treatment Secondary: Emergent adverse events	Perindopril/amlodipine reduced SBP by 20.3 mm Hg and perindopril reduced SBP by 16.9 mm Hg (P=0.009). Perindopril/amlodipine reduced DBP by 11.9 mm Hg and perindopril reduced DBP by 10.2 mm Hg (P=0.018). <u>Perindopril/amlodipine versus irbesartan</u> Perindopril/amlodipine reduced SBP by 14.1 mm Hg and irbesartan reduced SBP by 12.7 mm Hg (P=0.003). Perindopril/amlodipine reduced DBP by 5.8 mm Hg and irbesartan reduced DBP by 5.2 mm Hg (P=0.008). <u>Perindopril/amlodipine versus valsartan</u> Perindopril/amlodipine reduced SBP by 18 mm Hg and valsartan reduced SBP by 14.6 Hg (P<0.001). Perindopril/amlodipine reduced DBP by 13 mm Hg and valsartan reduced DBP by 11.2 mm Hg (P<0.001). There was a significant difference observed in the estimated treatment difference for SBP between perindopril/amlodipine and RAS-inhibitor monotherapy (estimated treatment difference, -2.36; 95% CI, -2.36 to -0.89; P=0.002). There was a significant difference observed in the estimated treatment difference for DBP between perindopril/amlodipine and RAS-inhibitor monotherapy (estimated treatment difference, -1.25; 95% CI, -2.12 to -0.38; P=0.005). Secondary: The proportion of patients who experienced emergent adverse events was similar for both perindopril/amlodipine (28.4%) and RAS-inhibitor monotherapy (28.2%) groups (P=0.929).
Renal Effects				
Esnault et al.[132]	MC, DB, PC, RCT	N=263	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2008) Amlodipine 5 to 10 mg QD vs enalapril 5 to 20 mg/day	Nondiabetic, adult patients with estimated creatinine clearance of 20 to 60 ml/min	3 years	Change in GFR measured yearly by blood clearance Secondary: Composite of renal events and tolerability	No statistically significant difference was found between amlodipine and enalapril in GFR decline (-4.92 and -3.98 mL/min., respectively, at last observation). Secondary: No statistically significant difference was found between amlodipine and enalapril in the composite secondary end point after a median follow-up of 2.9 years, including in the subgroup of patients with proteinuria >1 g/d at baseline.
Agodoa et al.[133] (2001) AASK Amlodipine 5 to 10 mg QD vs ramipril 2.5 to 10 mg QD	DB, MC, RCT African American patients, age 18 to 70 years old, with hypertensive renal disease (GFR 20 to 65 mL/min)	N=1,094 4 years	Primary: Rate of change in GFR (GFR slope) Secondary: Composite of: confirmed reduction GFR by 50% or by 25 mL/min for baseline, ESRD	Primary: The average decline in GFR was slower, by 36% in the ramipril group as compared to the amlodipine group (P=0.002). However, during the first three months, GFR increased more in the amlodipine group than the ramipril group (P<0.001). The mean total slope did not differ between the groups (P=0.38). Secondary: The risk reduction for the composite secondary outcome was significantly greater for the ramipril group than the amlodipine group (P=0.005). The rate of ESRD was significantly lower in the ramipril group (P=0.01).
Wright et al.[134] (2002) AASK Amlodipine 5 to 10 mg/day vs metoprolol 50 to 200 mg/day vs ramipril 2.5 to 10 mg/day	DB, MC, RCT Patients were self-identified African Americans aged 18 to 70 years with HTN and a GFR between 20 and 65 mL/min/ 1.73 m^2 and no other identified cause of renal insufficiency	N=1,094 3 to 6.4 years	Primary: Rate of change in GFR (grouped by usual blood pressure [MAP goal 102 to 107 mm Hg] vs lower blood pressure [≤92 mm Hg]) Secondary: Clinical composite outcome (reduction in GFR by 50% or more, ESRD, or death)	Primary: No significant difference in primary outcome was reported between the usual blood pressure group compared to the lower blood pressure group (P=0.24). None of the drug group comparisons showed consistently significant differences in the GFR slope. Secondary: The lower blood pressure goal did not significantly reduce the rate of the clinical composite outcome (risk reduction for lower blood pressure group, 2%; 95% CI, -22 to 21; P=0.85). Ramipril resulted in significant risk reductions in the clinical composite outcomes compared to amlodipine (38%; 95% CI, 14 to 56; P=0.004) and metoprolol (22%; 95% CI, 1 to 38; P=0.04).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was no significant difference in the clinical composite outcome between the amlodipine and metoprolol groups.
Lewis et al.[135] (2001) IDNT Amlodipine 10 mg/day vs irbesartan 300 mg/day vs placebo	DB, MC, PC, PRO, RCT Patients 30 to 70 years old, with type 2 diabetes mellitus, HTN, and nephropathy	N=1,715 2.6 years	Primary: Composite of risk of doubling serum creatinine, ESRD, or death from any cause Secondary: Composite of death from cardiovascular causes, nonfatal MI, heart failure requiring hospitalization, permanent neurologic deficit caused by a cerebrovascular event, or lower limb amputation	Primary: Compared to placebo, irbesartan 300 mg/day resulted in a 20% lower relative risk of the composite primary outcome (P=0.02). Irbesartan treatment was associated with a 33% lower risk of doubling serum creatinine (P=0.003) and 23% trend towards lower risk of ESRD (P=0.07) compared to placebo. There was no significant difference in risk of death from any cause for irbesartan compared to placebo (P=0.57). Compared to amlodipine, irbesartan treatment resulted in a 23% lower risk of composite primary outcome (P=0.006). Irbesartan treatment was associated with a 37% lower risk of doubling serum creatinine vs amlodipine (P<0.001) and 23% trend towards lower risk of ESRD vs amlodipine (P=0.07). There was no significant difference in risk of death from any cause (P=0.80). Secondary: There were no significant differences in the secondary cardiovascular composite end point (P=0.40 and P=0.79 for irbesartan vs placebo and amlodipine, respectively).
Viberti et al.[136] (2002) MARVAL Amlodipine 5 mg QD vs valsartan 80 mg QD A target blood pressure of 135/85 mm Hg was aimed	AC, DB, RCT Patients 35 to 75 years old with type 2 diabetes mellitus and microalbuminuria, with or without HTN	N=332 24 weeks	Primary: Change in UAER; proportion of patients who returned to normal albuminuria Secondary: Proportion of patients returning to normoalbuminuria	Primary: Valsartan resulted in a UAER reduction of 44% at 24 weeks compared to baseline vs an 8% reduction with amlodipine (P<0.001). Valsartan lowered UAER similarly in both the hypertensive and normotensive groups. Over the study period, blood pressure reductions were similar between the two treatments and at no time point was there a between-group significant difference in blood pressure values in either the hypertensive or the normotensive subgroup. Secondary: The proportion of patients returning to normal albuminuria was greater with valsartan (29.9%) vs amlodipine (14.5%; P=0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
for by dose-doubling followed by the addition of bendrofluazide* and doxazosin whenever needed.				
Bakris et al.[137] (2008) GUARD Amlodipine and benazepril (fixed-dose combination product) vs benazepril and HCTZ (fixed-dose combination product)	DB, RCT Hypertensive, albuminuric type 2 diabetic patients, mean age 58 years were randomized to receive either initial fixed-dose combination product	N=322 52 weeks	Primary: Change in urinary albumin to creatinine ratio after 1 year of initial treatment with either fixed-dose combination, blood pressure reductions Secondary: Proportion who progressed to overt diabetic nephropathy, safety	Primary: Both combinations significantly reduced the urinary albumin to creatinine ratio compared to baseline (P<0.0001). The median percent change was -72.1% for benazepril and HCTZ and -40.5% for amlodipine and benazepril (P<0.0001). Both regimens significantly reduced SBP and DBP compared to baseline (P<0.0001). The mean reduction in both SBP and DBP was greater in the amlodipine-based arm than in the HCTZ-based arm; however, significance in favor of the amlodipine regimen was observed only for DBP (SBP -20.5 vs -18.8; P=0.19; DPB -13.1 vs -9.97; P=0.02). A greater proportion of patients who had microalbuminuria at baseline and treated with benazepril and HCTZ compared to amlodipine and benazepril attained normalization of the urinary albumin to creatinine ratio, defined as <30 mg/g (69.2 vs 47.8%; P=0.0004). Secondary: The percentage of patients progressing to overt proteinuria was similar for both groups. Overall, both study drugs were well tolerated. Adverse reactions possibly related to the study medications occurred in 11.4 and 3.6% of patients receiving amlodipine and benazepril and benazepril and HCTZ, respectively. They included peripheral edema (7.8 vs 2.4%, respectively), fatigue (1.2% in each group), pitting edema (1.2 vs 0.0%), face edema (0.6 vs 0.0%) and thirst (0.6 vs 0.0%). More patients receiving the HCTZ-based regimen (10.8%) discontinued study drug than with the amlodipine-based regimen due to side effects (5.4%).
Casas et al.[138] (2005)	MA (127 trials)	N=not reported	Primary: Doubling of serum	Primary: Treatment with ACE inhibitors or ARBs resulted in a nonsignificant

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ACE inhibitor or ARBs compared to placebo vs ACE inhibitor or ARBs compared to other antihypertensive drugs (β-adrenergic blocking agents, α-adrenergic blocking agents, calcium-channel blocking agents, or combinations) Specific agents and doses were not specified.	Studies in adults that examined the effect of any drug treatment with a blood pressure lowering action on progression of renal disease	4.2 years (mean)	creatinine, and ESRD Secondary: Serum creatinine, urine albumin excretion and GFR	reduction in the risk of doubling of creatinine vs other antihypertensives (P=0.07) with no differences in the degree of change of SBP or DBP between the groups. A small reduction in ESRD was observed in patients receiving ACE inhibitors or ARBs compared to other antihypertensives (P=0.04) with no differences in the degree of change of SBP or DBP between the groups. Secondary: Small reductions in serum creatinine and in SBP were noted when ACE inhibitors or ARBs were compared to other antihypertensives (P=0.01). Small reduction in daily urinary albumin excretion in favor of ACE inhibitor or ARBs were reported when these agents were compared to other antihypertensives (P=0.001). Compared to other drugs, ACE inhibitors or ARBs had no effect on the GFR.
Miscellaneous				
Rosendorff et al.[139] (2009) Amlodipine 5 to 10 mg QD vs olmesartan 20 to 40 mg QD	AC, DB, RCT Adults with HTN and left ventricular hypertrophy	N=102 52 weeks	Primary: Change in left ventricular mass from baseline to 52 weeks Secondary: Change in left ventricular mass after 26 weeks of treatment	Primary: Mean±SD left ventricular masses of 252.9±73.06 g in the olmesartan group and 236.9±59.94 g in the amlodipine group at baseline were decreased to 248.2±69.31 and 223.9±53.18 g, respectively, after 52 weeks of therapy. Neither of these changes was significantly different from baseline, and the difference between the two treatment groups was not significant. Secondary: At 26 weeks, adjusted percent changes in left ventricular mass were 8.0% with olmesartan and 6.0% with amlodipine. Changes occurring at the 26-week assessment were not significantly different from baseline or from each other.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Luscher et al.[140] (2009) ENCORE II Nifedipine 30 to 60 mg QD vs placebo	DB, MC, PC, RCT Adults undergoing coronary angiography with or without PCI	N=226 18 to 24 months	Primary: The effect of nifedipine compared to placebo on acetylcholine-induced coronary vascular response at the highest dose of acetylcholine at baseline and follow-up Secondary: Effect of nifedipine on the percent change in plaque volume as assessed by intravascular ultrasound	Primary: The change in mean luminal diameter averaged 13.9±16.5% with nifedipine and 7.7±18% with placebo. The difference between groups was 6.3% (95% CI, 1.6 to 10.9; P=0.0088). Secondary: Neither the difference in absolute nor relative changes in mean plaque volume as measure by intravascular ultrasound between treatments was significant (P=0.84 and 0.66, respectively).
Schmid-Elsaesser et al.[141] (2006) Nimodipine continuous infusion of 1 mg/hr for 6 hours, followed by 2.0 mg/hr Vs magnesium sulfate bolus infusion 10 mg/kg, followed by continuous infusion of 30 mg/kg QD	RCT Patients with aneurismal subarachnoid hemorrhage	N=104 7 days	Primary: Incidence of clinical vasospasm and transcranial Doppler angiographic vasospasm, and infarction attributable to vasospasm Secondary: Incidence of angiographic vasospasm	Primary: There was no significant difference between the groups in number of patients experiencing clinical vasospasm or transcranial doppler/angiographic vasospasm: 14 patients (27%) in the nimodipine group vs eight patients (15%) in the magnesium group (P=0.193); 17 (33%) in the nimodipine group vs 20 (38%) in the magnesium group (P=0.792). No difference between the groups was found in incidence of cerebral infarction, 11 (22%) in the nimodipine group vs 10 (19%) in the magnesium group. Secondary: There were no significant differences in incidence of angiographic vasospasm, neuronal markers or Glasgow outcome scores (all values: P>0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Liu et al.[142] (abstract) (2011) Nimodipine vs placebo	MA (8 trials) Patients receiving prophylactic nimodipine for aneurismal subarachnoid hemorrhage	N=1,514 Not reported	Primary: Not reported Secondary: Not reported	Primary: Not reported Secondary: Not reported Compared to placebo, fully recovered (all cases) patients increased 64% with nimodipine (OR, 1.64; 95% CI, 1.26 to 2.13; P=0.002; NNT, -1.048), fully recovered or moderately disabled (all cases) patients increased 79% (OR, 1.79; 95% CI, 1.28 to 2.51; P=0.0007; NNT, -5.889), patient death (in cerebral vasospasm cases) decreased 74% (OR, 0.26; 95% CI, 0.09 to 0.71; P=0.008; NNT, 2.298), the incidence of symptomatic cerebral vasospasm decreased 46% (OR, 0.54; 95% CI, 0.42 to 0.69; P<0.00001; NNT, 1.952), the incidence of delayed neurological function deficits (all cases) decreased 38% (OR, 0.62; 95% CI 0.50 to 0.78; P<0.0001; NNT, 1.078), the occurrence of cerebral infarction (on CT scan) decreased 58% (OR, 0.58; 95% CI, 0.42 to 0.81; P=0.001; NNT, 3.314), the occurrence of cerebral infarction (in cerebral vasospasm cases) decreased 65% (OR, 0.35; 95% CI, 0.17 to 0.69; P=0.003; NNT, 3.688), and the occurrence of cerebral infarction (all cases) decreased 48% (OR, 0.52; 95% CI, 0.41 to 0.66; P<0.00001; NNT, 1.196). The difference in recurrent hemorrhage and adverse reactions between the nimodipine and placebo was not statistically significant (recurrent hemorrhage: OR, 0.75; 95% CI, 0.50 to 1.11; P=0.15; adverse reaction: OR, 1.13; 95% CI, 0.71 to 1.81; P = 0.59). Secondary: Not reported

*Agent not available in the United States.
Drug regimen abbreviations: BID=twice daily, CR=controlled-release, ER=extended-release, QD=once daily, SR=sustained-release
Study design abbreviations: AC=active comparator, DB=double blind, DD=double dummy, ES=extended-release, MA=meta analysis, MC=multicenter, OL=open label, OS=observational, PC=placebo controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, XO=cross over
Miscellaneous abbreviations: ACE inhibitor=angiotensin converting enzyme inhibitor, ABPM=ambulatory blood pressure monitoring, ARB=angiotensin II receptor blocker, BMI=body mass index, CAD=coronary artery disease, CHD=coronary heart disease, CHF=congestive heart failure, CI=confidence interval, CT=computed tomography, DBP=diastolic blood pressure, ECG=electrocardiogram, ESRD=end stage renal disease, FBG=fasting blood glucose, GFR=glomerular filtration rate, HbA_{1c}=glycosylated hemoglobin, HCTZ=hydrochlorothiazide, HDL-C=high-density lipoprotein cholesterol, HTN=hypertension, HR=hazard ratio, LDL-C=low-density lipoprotein cholesterol, MI=myocardial infarction, MMSE=Mini Mental State Examination, NIDDM=non-insulin dependent diabetes mellitus, NNT=number needed to treat, OR=odds ratio, PAD=peripheral artery disease, PCI=percutaneous coronary intervention, PVD=peripheral vascular disease, QOL=quality of life, RAS=renin-angiotensin system, RR=relative risk, SBP=systolic blood pressure, SD=standard deviation, TC=total cholesterol, TG=triglyceride, TIA=transient ischemic attack, UAER=urinary albumin excretion rate

Additional Evidence

Dose Simplification
Taylor et al. evaluated adherence rates in patients receiving a fixed-dose combination of amlodipine and benazepril compared to patients receiving an ACE inhibitor and a long-acting dihydropyridine calcium-channel blocking agent as separate formulations. There was no significant difference in adherence in younger subjects (18 to 39 year olds); however, overall adherence was higher in patients receiving amlodipine/benazepril fixed-dose combination product compared to those receiving separate formulations (80.8 vs 73.8%; P<0.001).[143] Dickson et al. also evaluated adherence rates with the fixed-dose combination of amlodipine/benazepril compared to the administration of an ACE inhibitor and dihydropyridine calcium-channel blocking agent as separate formulations in an elderly Medicaid population. Over a 12 month period, adherence rates were higher in patients receiving the fixed-dose combination product compared to those receiving separate formulations (63.4 vs 49.0%; P<0.0001).[144] Gerbino et al. assessed adherence rates in patients receiving the fixed-dose combination of amlodipine/benazepril or an ACE inhibitor and dihydropyridine calcium-channel blocking agent administered as separate formulations. Adherence rates were 69.2% for patients who received the antihypertensive agents as separate formulations compared to 87.9% for patients receiving the fixed-dose combination product (P<0.0001).[145]

Stable Therapy
Lenz et al. compared the 24-hour blood pressure control in patients stabilized on amlodipine who were then converted to nisoldipine. After three months, blood pressure control was similar between treatments, except for average 24-hour diastolic blood pressure, where nisoldipine treatment resulted in slightly greater readings (by 2 mm Hg).[69] Gustin et al. reviewed medical records of hypertensive patients who were switched from long-acting nifedipine to felodipine. This resulted in slightly lower diastolic blood pressure measurements (78 vs 80 mm Hg; P<0.05). Adverse events and supplemental medication use were similar between the agents.[124] Sapienza et al. measured the impact of converting long-term care patients previously on high dose calcium-channel blocking agents or dual therapy with an ACE inhibitor and calcium-channel blocking agents to the fixed-dose combination of amlodipine/benazepril. There was no significant change in blood pressure following the conversion; however, there was a significant reduction in the number of patients reporting ≥1 drug-related adverse event (22 vs 4; P<0.05).[146]

Impact on Physician Visits
Sheehy et al. conducted a comparative review of patients receiving amlodipine or felodipine. The investigators found an increased number of specialist visits in the amlodipine group (odds ratio, 1.14; 95% confidence interval, 18 to 1.20); however, this same group of patients receiving amlodipine had significantly better compliance and refill rates and fewer medication switches.[60]

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 15. Relative Cost of the Dihydropyridines

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Amlodipine	solution, suspension, tablet	Katerzia®, Norliqva®, Norvasc®*	$$$$$	$
Felodipine	extended-release tablet	N/A	N/A	$
Isradipine	capsule	N/A	N/A	$$$$$
Levamlodipine	tablet	N/A	N/A	$$$
Nicardipine	capsule*, injection*	N/A	N/A	$$$$$
Nifedipine	capsule, extended-release tablet	Adalat CC®*, Procardia XL®*	$$$$$	$
Nimodipine	capsule*, solution	Nymalize®	$$$$$	$$$$$
Nisoldipine	extended-release tablet*	Sular ER®*	$$$$$	$$$$$
Combination Products				
Amlodipine and benazepril	capsule	Lotrel®*	$$$$$	$
Amlodipine and olmesartan	tablet	Azor®*	$$$$$	$
Amlodipine and valsartan	tablet	Exforge®*	$$$$$	$$
Amlodipine, valsartan, and HCTZ	tablet	Exforge HCT®*	$$$$$	$$$$$

*Generic is available in at least one dosage form or strength.
HCTZ=hydrochlorothiazide, N/A=not available

X. Conclusions

All of the dihydropyridines, with the exception of nimodipine, are approved for the treatment of hypertension. Amlodipine, nicardipine, and nifedipine are also indicated for the treatment of angina. Additionally, amlodipine reduces the risk of hospitalization due to angina and reduces the risk of coronary revascularization procedures in patients with recently documented coronary artery disease.[1,2,5-17] Amlodipine is available in combination with benazepril, olmesartan, valsartan, or valsartan-hydrochlorothiazide. It should be noted that the amlodipine and telmisartan fixed-dose combination product and the amlodipine, olmesartan, and hydrochlorothiazide fixed-dose combination product are included in the angiotensin II receptor antagonists class review (AHFS Class 243208). All of the products with the exception of clevidipine are available in a generic formulation.

There are several national and international guidelines that provide recommendations regarding the use of calcium-channel blocking agents.[18-34] For the treatment of chronic angina, β-blockers are recommended as initial therapy; however, long-acting calcium-channel blocking agents may be used if β-blockers are contraindicated or if additional therapy is required.[18-22] Calcium-channel blocking agents are recommended as initial therapy in patients with variant/vasospastic angina.[19] For the treatment of heart failure, ACE inhibitors, ARBs, aldosterone antagonists, and isosorbide dinitrate/hydralazine are recommended as initial therapy. In general, calcium-channel blocking agents are not recommended in the management of heart failure.[24-25] There are several published guidelines on the treatment of hypertension. Thiazide-type diuretics are frequently recommended as initial therapy

in patients with uncomplicated hypertension.[26-32] According to the National Heart, Lung, and Blood Institute's Eighth Report of The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8), thiazide-type diuretics should be utilized first-line for most patients with hypertension, either alone or in combination with another hypertensive from a different medication class (e.g., ACE inhibitors, ARBs, β-blockers, calcium channel blockers).[26] Several guidelines consistently recommend that the selection of an antihypertensive agent be based on compelling indications for use.[26-32,34] Most patients will require more than one antihypertensive medication to achieve blood pressure goals.[26-32,34]

Numerous clinical trials have shown that the dihydropyridines can effectively lower systolic and diastolic blood pressure when administered alone or in combination with other agents. In trials comparing combination therapy to monotherapy, the more aggressive treatment regimens lowered blood pressure to a greater extent than the less-intensive treatment regimens. Some comparative trials have demonstrated slight differences in blood pressure effects among the various dihydropyridines; however, the clinical significance of these differences remains to be established.[60-130] Most patients will require more than one antihypertensive agent to achieve blood pressure goals.[26-32] The use of a fixed-dose combination product may simplify the treatment regimen and improve adherence.[28,29,143-145] However, there are no prospective, randomized trials that have demonstrated better clinical outcomes with a fixed-dose combination product compared to the coadministration of the individual components as separate formulations. The dihydropyridines have been shown to favorably affect cardiovascular morbidity and mortality, and several studies have demonstrated comparable efficacy with β-blockers, diuretics, ACE inhibitors, ARBs.[37-59]

There is insufficient evidence to support that one brand dihydropyridine is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand dihydropyridines within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand dihydropyridine is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Calcium-Channel Blocking Agents, Miscellaneous
AHFS Class 242892
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I. Overview

The movement of calcium ions is essential for the function of all types of muscle, including cardiac and vascular smooth muscle. When this flow is reduced, the result is a weakening of muscle contraction and relaxation of muscle tissue.[1-3] Relaxation of coronary vascular smooth muscle increases the flow of oxygenated blood into the myocardium, while relaxation of arteriolar smooth muscle decreases peripheral vascular resistance. Both coronary and systemic vasodilation serve to reduce cardiac workload. The calcium-channel blocking agents include dihydropyridines and miscellaneous agents (nondihydropyridines). Although they have different binding sites on the L-type calcium channel, both block the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. The nondihydropyridines also block the T-type calcium channel in the atrioventricular node.[1-4]

The miscellaneous calcium-channel blocking agents include diltiazem and verapamil, which are approved for the treatment of angina, arrhythmias, and hypertension.[1,2,5-12] Diltiazem is a potent coronary vasodilator, but is only a mild arterial vasodilator. Although it decreases atrioventricular (AV) node conduction, diltiazem does not have negative inotropic properties.[1,2,5-12] Verapamil dilates coronary and peripheral arteries. It also slows conduction through the AV node, and has negative inotropic and chronotropic effects.[1,2,5-12] Both diltiazem and verapamil are available in a variety of modified-release delivery systems that alter their pharmacokinetic properties, including onset and duration of action.[1,2]

The miscellaneous calcium-channel blocking agents that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Diltiazem and verapamil are available in generic formulations. This class was last reviewed in May 2022.

Table 1. Calcium-Channel Blocking Agents, Miscellaneous Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Diltiazem	extended-release capsule, extended-release tablet, injection, tablet	Cardizem®*, Cardizem CD®*, Cardizem LA®*, Matzim LA®*, Tiazac®*	diltiazem
Verapamil	extended-release capsule, extended-release tablet, injection, tablet	Calan SR®*, Verelan®*, Verelan PM®*	verapamil

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the miscellaneous calcium-channel blocking agents are summarized in Table 2.

Table 2. Treatment Guidelines Using the Calcium-Channel Blocking Agents, Miscellaneous

Clinical Guideline	Recommendations
American Heart Association/American College of Cardiology/ American College of Clinical Pharmacy/American Society for	• In patients with chronic coronary disease (CCD), high-intensity statin therapy is recommended with the aim of achieving a ≥50% reduction in LDL-C levels to reduce the risk of major adverse cardiovascular events (MACE). • In patients in whom high-intensity statin therapy is contraindicated or not tolerated, moderate-intensity statin therapy is recommended with the aim of achieving a 30% to 49% reduction in LDL-C levels to reduce the risk of MACE. • In patients with CCD who are judged to be at very high risk and on maximally tolerated statin therapy with an LDL-C level ≥70 mg/dL, ezetimibe can be

Clinical Guideline	Recommendations
Preventive Cardiology/National Lipid Association/ Preventive Cardiovascular Nurses Association **Guideline for the Management of Patients With Chronic Coronary Disease (2023)**[13]	beneficial to further reduce the risk of MACE. • In patients with CCD who are judged to be at very high risk and who have an LDL-C level ≥70 mg/dL, or a non–high-density lipoprotein cholesterol (HDL-C) level ≥100 mg/dL, on maximally tolerated statin and ezetimibe, a PCSK9 monoclonal antibody can be beneficial to further reduce the risk of MACE. • In patients with CCD on maximally tolerated statin therapy with an LDL-C level <100 mg/dL and a persistent fasting triglyceride level of 150 to 499 mg/dL after addressing secondary causes, icosapent ethyl may be considered to further reduce the risk of MACE and cardiovascular death. • In patients with CCD who are not at very high risk and on maximally tolerated statin therapy with an LDL-C level ≥70 mg/dL, it may be reasonable to add ezetimibe to further reduce the risk of MACE. • In patients with CCD on maximally tolerated statin therapy who have an LDL-C level ≥70 mg/dL, and in whom ezetimibe and PCSK9 monoclonal antibody are deemed insufficient or not tolerated, it may be reasonable to add bempedoic acid or inclisiran (in place of PCSK9 monoclonal antibody) to further reduce LDL-C levels. • In patients with CCD receiving statin therapy, adding niacin, fenofibrate, or dietary supplements containing omega-3 fatty acids are not beneficial in reducing cardiovascular risk. • In adults with CCD, nonpharmacologic strategies are recommended as first-line therapy to lower BP in those with elevated BP (120-129/<80 mmHg). • In adults with CCD who have hypertension, a BP target of <130/<80 mmHg is recommended to reduce CVD events and all-cause death. • In adults with CCD and hypertension (systolic BP ≥130 and/or diastolic BP ≥80 mm Hg), in addition to nonpharmacological strategies, GDMT angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), or beta blockers are recommended as first-line therapy for compelling indications (e.g., recent MI or angina), with additional antihypertensive medications (e.g., dihydropyridine calcium channel blockers [CCB], long-acting thiazide diuretics, and/or mineralocorticoid receptor antagonists) added as needed to optimize BP control. • In patients with CCD and no indication for oral anticoagulant therapy, low-dose aspirin 81 mg (75 to 100 mg) is recommended to reduce atherosclerotic events. • In patients with CCD treated with PCI, dual antiplatelet therapy (DAPT) consisting of aspirin and clopidogrel for 6 months post PCI followed by single antiplatelet therapy (SAPT) is indicated to reduce MACE and bleeding events.* • In select patients with CCD treated with PCI and a drug-eluting stent (DES) who have completed a 1- to 3-month course of DAPT, P2Y12 inhibitor monotherapy for at least 12 months is reasonable to reduce bleeding risk. • In patients with CCD who have had a previous MI and are at low bleeding risk, extended DAPT beyond 12 months for a period of up to 3 years may be reasonable to reduce MACE. • In patients with CCD and a previous history of MI without a history of stroke, transient ischemic attack (TIA), or ICH, vorapaxar may be added to aspirin therapy to reduce MACE. • In patients with CCD, the use of DAPT after CABG may be useful to reduce the incidence of saphenous vein graft occlusion. • In patients with CCD without recent ACS or a PCI-related indication for DAPT, the addition of clopidogrel to aspirin therapy is not useful to reduce MACE. • In patients with CCD and previous stroke, TIA, or ICH, vorapaxar should not be added to DAPT because of increased risk of major bleeding and ICH. • In patients with CCD and previous stroke, TIA, or ICH, prasugrel should not be used because of risk of significant or fatal bleeding. • In patients with CCD, chronic nonsteroidal anti-inflammatory drugs should not be

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	used because of increased cardiovascular and bleeding complications. • In patients with CCD who have undergone elective PCI and who require oral anticoagulant therapy, DAPT for one to four weeks followed by clopidogrel alone for six months should be administered in addition to DOAC. • In patients with CCD who have undergone PCI and who require oral anticoagulant therapy, continuing aspirin in addition to clopidogrel for up to 1 month is reasonable if the patient has a high thrombotic risk and low bleeding risk. • In patients with CCD who require oral anticoagulation and have a low atherothrombotic risk, discontinuation of aspirin therapy with continuation of DOAC alone may be considered one year after PCI to reduce bleeding risk. • In patients with CCD who require oral anticoagulation, DOAC monotherapy may be considered if there is no acute indication for concomitant antiplatelet therapy. • In patients with CCD without an indication for therapeutic DOAC or DAPT and who are at high risk of recurrent ischemic events but low-to-moderate bleeding risk, the addition of low-dose rivaroxaban 2.5 mg twice daily to aspirin 81 mg daily is reasonable for long-term reduction of risk for MACE. • In patients with CCD on DAPT, the use of a PPI can be effective in reducing gastrointestinal bleeding risk. • In patients with CCD and LVEF ≤40% with or without previous MI, the use of beta-blocker therapy is recommended to reduce the risk of future MACE, including cardiovascular death. • In patients with CCD and LVEF<50%, the use of sustained release metoprolol succinate, carvedilol, or bisoprolol with titration to target doses is recommended in preference to other beta blockers. • In patients with CCD who were initiated on beta-blocker therapy for previous MI without a history of or current LVEF ≤50%, angina, arrhythmias, or uncontrolled hypertension, it may be reasonable to reassess the indication for long-term (>1 year) use of beta-blocker therapy for reducing MACE. • In patients with CCD without previous MI or LVEF ≤50%, the use of beta-blocker therapy is not beneficial in reducing MACE, in the absence of another primary indication for beta-blocker therapy. • In patients with CCD who also have hypertension, diabetes, LVEF ≤40%, or CKD, the use of ACE inhibitors, or ARBs if ACE inhibitor–intolerant, is recommended to reduce cardiovascular events. • In patients with CCD without hypertension, diabetes, or CKD and LVEF >40%, the use of ACE inhibitors or ARBs may be considered to reduce cardiovascular events. • In patients with CCD, the addition of colchicine for secondary prevention may be considered to reduce recurrent ASCVD events. • In patients with CCD, an annual influenza vaccination is recommended to reduce cardiovascular morbidity, cardiovascular death, and all-cause death. • In patients with CCD, coronavirus disease 2019 (COVID-19) vaccination is recommended per public health guidelines to reduce COVID-19 complications. • In patients with CCD, a pneumococcal vaccine is reasonable to reduce cardiovascular morbidity and mortality and all-cause death. • In patients with CCD and angina, antianginal therapy with either a beta blocker, CCB, or long-acting nitrate is recommended for relief of angina or equivalent symptoms. • In patients with CCD and angina who remain symptomatic after initial treatment, addition of a second antianginal agent from a different therapeutic class (beta blockers, CCB, long-acting nitrates) is recommended for relief of angina or equivalent symptoms. • In patients with CCD, ranolazine is recommended in patients who remain symptomatic despite treatment with beta blockers, CCB, or long-acting nitrate therapies. • In patients with CCD, sublingual nitroglycerin or nitroglycerin spray is

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	recommended for immediate short-term relief of angina or equivalent symptoms. • In patients with CCD and normal LV function, the addition of ivabradine to standard anti-anginal therapy is potentially harmful. • In patients with CCD and lifestyle-limiting angina despite GDMT and with significant coronary artery stenoses amenable to revascularization, revascularization is recommended to improve symptoms. • In patients with CCD who have experienced SCAD, beta-blocker therapy may be reasonable to reduce the incidence of recurrent SCAD. • Women with CCD who are contemplating pregnancy or who are pregnant should not use ACE inhibitors, ARBs, direct renin inhibitors, angiotensin receptor-neprilysin inhibitors, or aldosterone antagonists during pregnancy to prevent harm to the fetus. • Women with CCD should not receive systemic postmenopausal hormone therapy because of a lack of benefit on MACE and mortality, and an increased risk of venous thromboembolism.
European Society of Cardiology: **Guidelines for the Diagnosis and Management of Chronic Coronary Syndromes (2019)**[14]	<u>Pharmacological management of stable coronary artery disease (CAD) patients</u> • The two aims of the pharmacological management of stable CAD patients are to obtain relief of symptoms and to prevent CV events. • Optimal medical treatment indicates at least one drug for angina/ischaemia relief plus drugs for event prevention. • It is recommended to educate patients about the disease, risk factors and treatment strategy. • It is indicated to review the patient's response soon after starting therapy. • Concomitant use of a proton pump inhibitor is recommended in patients receiving aspirin monotherapy, DAPT, or DOAC monotherapy who are at high risk of gastrointestinal bleeding. • Lipid-lowering drugs: if goals are not met on maximum tolerated dose of a statin, consideration of combination therapy with ezetimibe or a PCSK9 inhibitor is recommended • ACE inhibitors should be considered in patients at a very high risk of cardiovascular adverse events • Angina/ischemia relief: o Short-acting nitrates are recommended. o First-line treatment is indicated with ß-blockers and/or calcium channel blockers to control heart rate and symptoms. o Long-acting nitrates should be considered as a second-line treatment option when initial therapy with a beta-blocker and/or a non-DHP-calcium channel blocker is contraindicated, poorly tolerated, or inadequate in controlling angina symptoms o Nicorandil, ranolazine, ivabradine, or trimetazidine should be considered as a second-line treatment to reduce angina frequency and improve exercise tolerance in subjects who cannot tolerate, have contraindications to, or whose symptoms are not adequately controlled by beta-blockers, CCBs, and long-acting nitrates. o According to comorbidities/tolerance, it is indicated to use second-line therapies as first-line treatment in selected patients. o In asymptomatic patients with large areas of ischaemia (>10%) ß-blockers should be considered. o In patients with vasospastic angina, calcium channel blockers and nitrates should be considered and β-blockers avoided. • Event prevention: o Low-dose aspirin daily is recommended in all stable CAD patients. o Clopidogrel is indicated as an alternative in case of aspirin intolerance. o Statins are recommended in all stable CAD patients. o It is recommended to use ACE inhibitors (or ARBs) if presence of other

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	conditions (e.g., heart failure, hypertension or diabetes). <u>Treatment in patients with microvascular angina</u> • It is recommended that all patients receive secondary prevention medications including aspirin and statins. • ß-blockers are recommended as a first-line treatment. • Calcium antagonists are recommended if ß-blockers do not achieve sufficient symptomatic benefit or are not tolerated. • ACE inhibitors or nicorandil may be considered in patients with refractory symptoms. • Xanthine derivatives or nonpharmacological treatments such as neurostimulatory techniques may be considered in patients with symptoms refractory to the above listed drugs. <u>Stenting and peri-procedural antiplatelet strategies in stable CAD patients</u> • Drug-eluting stent (DES) is recommended in stable CAD patients undergoing stenting if there is no contraindication to prolonged dual antiplatelet therapy (DAPT). • Aspirin is recommended for elective stenting. • Clopidogrel is recommended for elective stenting. • Prasugrel or ticagrelor should be considered in patients with stent thrombosis on clopidogrel without treatment interruption. • GP IIb/IIIa antagonists should be considered for bailout situation only. • Platelet function testing or genetic testing may be considered in specific or high-risk situations (e.g., prior history of stent thrombosis; compliance issue; suspicion of resistance; high bleeding risk) if results may change the treatment strategy. • Prasugrel or ticagrelor may be considered in specific high-risk situations of elective stenting (e.g., left main stenting, high risk of stent thrombosis, diabetes). • Pretreatment with clopidogrel (when coronary anatomy is not known) is not recommended. • Routine platelet function testing (clopidogrel and aspirin) to adjust antiplatelet therapy before or after elective stenting is not recommended. • Prasugrel or ticagrelor is not recommended in low-risk elective stenting. • After uncomplicated PCI, early cessation (≤1 week) of aspirin, and continuation of dual therapy with oral anticoagulation therapy and clopidogrel should be considered if the risk of stent thrombosis is low • Triple therapy with aspirin, clopidogrel, and a DOAC for ≥1 month should be considered when the risk of stent thrombosis outweighs the bleeding risk, with a total of no more than six months <u>Follow-up of revascularized stable coronary artery disease patients</u> • It is recommended that all revascularized patients receive a secondary prevention and be scheduled for follow-up visit. • It is recommended to instruct patients before discharge about return to work and reuptake of full activities. Patients have to be advised to seek immediate medical contact if symptoms (re-) occur. • Single antiplatelet therapy, usually aspirin, is recommended indefinitely. • DAPT is indicated after bare metal stent (BMS) for at least one month. • DAPT is indicated for six to 12 months after second generation DES. • DAPT may be used for more than one year in patients at high ischemic risk (e.g., stent thrombosis, recurrent acute coronary syndrome on DAPT, post MI/diffuse CAD) and low bleeding risk. • DAPT for one to three months may be used after DES implantation in patients at high bleeding risk or with undeferrable surgery or concomitant anticoagulant treatment.

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	Antithrombotic therapy in patients with chronic coronary syndrome: • Addition of a second antithrombotic drug to aspirin for long-term secondary prevention should be considered in patients with at least a moderately increased risk of ischemic events and without high bleeding risk • When oral anticoagulation is initiated in patients with AF, a DOAC is recommended in preference to VKA therapy.
American College of Physicians/ American College of Cardiology Foundation/ American Heart Association/ American Association for Thoracic Surgery/ Preventive Cardiovascular Nurses Association/ Society of Thoracic Surgeons: **Management of Stable Ischemic Heart Disease (2012)[15]**	Medical therapy to prevent MI and death in patients with stable IHD • Aspirin 75 to 162 mg daily should be continued indefinitely in the absence of contraindications. • Treatment with clopidogrel is a reasonable option when aspirin in contraindicated. • Dipyridamole should not be used as antiplatelet therapy. • Beta-blocker therapy should be initiated and continued for three years in all patients with normal left ventricular (LV) function following MI or acute coronary syndromes. • Metoprolol succinate, carvedilol, or bisoprolol should be used for all patients with systolic LV dysfunction (ejection fraction ≤40%) with heart failure or prior MI, unless contraindicated. • ACE inhibitors should be prescribed in all patients with stable IHD who also have hypertension, diabetes, LV systolic dysfunction (ejection fraction ≤40%), and/or chronic kidney disease, unless contraindicated. • Angiotensin-receptor blockers (ARBs) are recommended for patients with stable IHD who have hypertension, diabetes, LV systolic dysfunction, or chronic kidney disease and have indications for, but are intolerant of, ACE inhibitors. • Patients should receive an annual influenza vaccine. Medical therapy for relief of symptoms in patients with stable IHD • Beta-blockers are recommended as initial therapy for relief of symptoms. • Calcium channel blockers or long-acting nitrates should be prescribed for relief of symptoms when β-blockers are contraindicated or cause unacceptable side effects. • Calcium channel blockers or long-acting nitrates, in combination with β-blockers, should be prescribed for relief of symptoms when initial treatment with β-blockers is unsuccessful. • Nitroglycerin or nitroglycerin spray should be used for immediate relief of angina. • Ranolazine is a fourth-line agent reserved for patients who have contraindications to, do not respond to, or cannot tolerate β-blockers, calcium-channel blockers, or long-acting nitrates.

American College of Cardiology Foundation/ American Heart Association: **2014 American Heart Association/ American College of Cardiology Foundation Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes (2014)[16]**	Early hospital care- standard medical therapies
	• Supplemental oxygen should be administered to patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) with arterial oxygen saturation <90%, respiratory distress, or other high risk features of hypoxemia.
	• Anti-ischemic and analgesic medications
	  ○ Nitrates
	  ▪ Patients with NSTE-ACS with continuing ischemic pain should receive sublingual nitroglycerin (0.3 to 0.4 mg) every 5 minutes for up to three doses, after which an assessment should be made about the need for intravenous nitroglycerin.
	  ▪ Intravenous nitroglycerin is indicated for patients with NSTE-ACS for the treatment of persistent ischemia, heart failure, or hypertension.
	  ▪ Nitrates should not be administered to patients who recently received a phosphodiesterase inhibitor, especially within 24 hours of sildenafil or vardenafil, or within 48 hours of tadalafil.
	  ○ Analgesic therapy
	  ▪ In the absence of contraindications, it may be reasonable to administer morphine sulphate intravenously to patients with NSTE-ACE if there is

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	continued ischemic chest pain despite treatment with maximally tolerated anti-ischemic medications. ▪ Nonsteroidal anti-inflammatory drugs (NSAIDs) (except aspirin) should not be initiated and should be discontinued during hospitalization due to the increased risk of major adverse cardiac event associated with their use o Beta-adrenergic blockers ▪ Oral β-blocker therapy should be initiated within the first 24 hours in patients who do not have any of the following: 1) signs of HF, 2) evidence of low-output state, 3) increased risk for cardiogenic shock, or 4) other contraindications to β-blockade (e.g., PR interval >0.24 second, second- or third-degree heart block without a cardiac pacemaker, active asthma, or reactive airway disease) ▪ In patients with concomitant NSTE-ACS, stabilized heart failure, and reduced systolic function, it is recommended to continue β-blocker therapy with one of the three drugs proven to reduce mortality in patients with heart failure: sustained-release metoprolol succinate, carvedilol, or bisoprolol. ▪ Patients with documented contraindications to β-blockers in the first 24 hours should be re-evaluated to determine subsequent eligibility. o Calcium channel blockers (CCBs) ▪ In patients with NSTE-ACS, continuing or frequently recurring ischemia, and a contraindication to β-blockers, a nondihydropyridine CCB (e.g., verapamil or diltiazem) should be given as initial therapy in the absence of clinically significant LV dysfunction, increased risk for cardiogenic shock, PR interval >0.24 seconds, or second or third degree atrioventricular block without a cardiac pacemaker. ▪ Oral nondihydropyridine calcium antagonists are recommended in patients with NSTE-ACS who have recurrent ischemia in the absence of contraindications, after appropriate use of β-blockers and nitrates. ▪ CCBs are recommended for ischemic symptoms when β-blockers are not successful, are contraindicated, or cause unacceptable side effects. ▪ Long-acting CCBs and nitrates are recommended in patients with coronary artery spasm. ▪ Immediate-release nifedipine should not be administered to patients with NSTE-ACS in the absence of β-blocker therapy. o Other anti-ischemic interventions ▪ Ranolazine is currently indicated for treatment of chronic angina; however, it may also improve outcomes in NSTE-ACS patients due to a reduction in recurrent ischemia. o Cholesterol management ▪ High-intensity statin therapy should be initiated or continued in all patients with NSTE-ACS and no contraindications to its use. Treatment with statins reduces the rate of recurrent MI, coronary heart disease mortality, need for myocardial revascularization, and stroke. ▪ It is reasonable to obtain a fasting lipid profile in patients with NSTE-ACS, preferably within 24 hours of presentation. • Inhibitors of renin-angiotensin-aldosterone system o ACE inhibitors should be started and continued indefinitely in all patients with LVEF <0.40 and in those with hypertension, diabetes mellitus, or stable CKD, unless contraindicated. o ARBs are recommended in patients with heart failure or myocardial infarction with LVEF <0.40 who are ACE inhibitor intolerant. o Aldosterone-blockade is recommended in patients post-MI without significant renal dysfunction (creatinine >2.5 mg/dL in men or >2.0 mg/dL in women) or hyperkalemia (K >5.0 mEq/L) who are receiving therapeutic doses of ACE inhibitor and β-blocker and have a LVEF <0.40, diabetes mellitus, or heart

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	failure. • Initial antiplatelet/anticoagulant therapy in patients with definite or likely NSTE-ACS treated with an initial invasive or ischemia-guided strategy o Non-enteric coated, chewable aspirin (162 to 325 mg) should be given to all patients with NSTE-ACS without contraindications as soon as possible after presentation, and a maintenance dose of aspirin (81 to 162 mg/day) should be continued indefinitely. o In patients who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance, a loading dose of clopidogrel followed by a daily maintenance dose should be administered. o A $P2Y_{12}$ receptor inhibitor (clopidogrel or ticagrelor) in addition to aspirin should be administered for up to 12 months to all patients with NSTE-ACS without contraindications who are treated with an early invasive or ischemia-guided strategy. Options include: ▪ Clopidogrel: 300 or 600 mg loading dose, then 75 mg daily. ▪ Ticagrelor: 180 mg loading dose, then 90 mg twice daily. ▪ It is reasonable to use ticagrelor in preference to clopidogrel for $P2Y_{12}$ treatment in patients with NSTE-ACS who undergo an early invasive or ischemia-guided strategy. ▪ In patients with NSTE-ACS treated with an early invasive strategy and dual antiplatelet therapy (DAPT) with intermediate/high-risk features (e.g., positive troponin), a GP Iib/IIIa inhibitor may be considered as part of initial antiplatelet therapy. Preferred options are eptifibatide or tirofiban. <u>Percutaneous coronary intervention (PCI)- Antiplatelet and anticoagulant therapy</u> • Antiplatelet agents o Patients already taking daily aspirin before PCI should take 81 to 325 mg non-enteric coated aspirin before PCI o Patients not on aspirin therapy should be given non-enteric coated aspirin 325 mg as soon as possible before PCI. o After PCI, aspirin should be continued indefinitely. o A loading dose of a $P2Y_{12}$ inhibitor should be given before the procedure in patients undergoing PCI with stenting. Options include clopidogrel 600 mg, prasugrel 60 mg, or ticagrelor 180 mg. o In patients with NSTE-ACS and high-risk features (e.g., elevated troponin) not adequately pretreated with clopidogrel or ticagrelor, it is useful to administer a GP Iib/IIIa inhibitor (abciximab, double-bolus eptifibatide, or high-dose bolus tirofiban) at the time of PCI. o In patients receiving a stent (bare metal or drug eluting) during PCI, $P2Y_{12}$ inhibitor therapy should be given for at least 12 months. Options include clopidogrel 75 mg daily, prasugrel 10 mg daily, or ticagrelor 90 mg twice daily. • Anticoagulant therapy o An anticoagulant should be administered to patients with NSTE-ACS undergoing PCI to reduce the risk of intracoronary and catheter thrombus formation. o Intravenous unfractionated heparin (UFH) is useful in patients with NSTE-ACS undergoing PCI. o Bivalirudin is useful as an anticoagulant with or without prior treatment with UFH. o An additional dose of 0.3 mg/kg intravenous enoxaparin should be administered at the time of PCI to patients with NSTE-ACS who have received fewer than two therapeutic subcutaneous doses or received the last subcutaneous enoxaparin dose eight to 12 hours before PCI. o If PCI is performed while the patient is on fondaparinux, an additional 85

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	IU/kg of UFH should be given intravenously immediately before PCI because of the risk of catheter thrombosis (60 IU/kg IV if a GP Iib/IIIa inhibitor used with UFH dosing based on the target-activated clotting time). o Anticoagulant therapy should be discontinued after PCI unless there is a compelling reason to continue. • Timing of CABG in relation to use of antiplatelet agents o Non-enteric coated aspirin (81 to 325 mg daily) should be administered preoperatively to patients undergoing CABG. o In patients referred for elective CABG, clopidogrel and ticagrelor should be discontinued for at least five days before surgery and prasugrel for at least seven days before surgery. o In patients referred for urgent CABG, clopidogrel and ticagrelor should be discontinued for at least 24 hours to reduce major bleeding. o In patients referred for CABG, short-acting intravenous GP Iib/IIIa inhibitors (eptifibatide or tirofiban) should be discontinued for at least 2 to 4 hours before surgery and abciximab for at least 12 hours before to limit blood loss and transfusion. <u>Late hospital care, hospital discharge, and posthospital discharge care</u> • Medications at discharge o Medications required in the hospital to control ischemia should be continued after hospital discharge in patients with NSTE-ACS who do not undergo coronary revascularization, patients with incomplete or unsuccessful revascularization, and patients with recurrent symptoms after revascularization. Titration of the doses may be required. o All patients who are post–NSTE-ACS should be given sublingual or spray nitroglycerin with verbal and written instructions for its use. o Before hospital discharge, patients with NSTE-ACS should be informed about symptoms of worsening myocardial ischemia and MI and should be given verbal and written instructions about how and when to seek emergency care for such symptoms. o Before hospital discharge, patients who are post–NSTE-ACS and/or designated responsible caregivers should be provided with easily understood and culturally sensitive verbal and written instructions about medication type, purpose, dose, frequency, side effects, and duration of use. o For patients who are post–NSTE-ACS and have initial angina lasting more than one minute, nitroglycerin (one dose sublingual or spray) is recommended if angina does not subside within three to five minutes; call 9-1-1 immediately to access emergency medical services. o If the pattern or severity of angina changes, suggesting worsening myocardial ischemia (e.g., pain is more frequent or severe or is precipitated by less effort or occurs at rest), patients should contact their clinician without delay to assess the need for additional treatment or testing. o Before discharge, patients should be educated about modification of cardiovascular risk factors. • Late hospital and post-hospital oral antiplatelet therapy o Aspirin should be continued indefinitely. The dose should be 81 mg daily in patients treated with ticagrelor and 81 to 325 mg daily in all other patients. o In addition to aspirin, a $P2Y_{12}$ inhibitor (either clopidogrel or ticagrelor) should be continued for up to 12 months in all patients with NSTE-ACS without contraindications who are treated with an ischemia-guided strategy. o In patients receiving a stent (bare-metal stent or DES) during PCI for NSTE-ACS, P2Y12 inhibitor therapy should be given for at least 12 months. • Combined oral anticoagulant therapy and antiplatelet therapy in patients with NSTE-ACS o The duration of triple antithrombotic therapy with a vitamin K antagonist,

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	aspirin, and a $P2Y_{12}$ receptor inhibitor in patients with NSTE-ACS should be minimized to the extent possible to limit the risk of bleeding. ○ Proton pump inhibitors should be prescribed in patients with NSTE-ACS with a history of gastrointestinal bleeding who require triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a $P2Y_{12}$ receptor inhibitor.
European Society of Cardiology: **Guidelines for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation (2020)**[17]	<u>Pharmacological treatment of ischemia</u> • Sublingual or intravenous nitrates and early initiation of β-blocker treatment is recommended in patients with ongoing ischemic symptoms and without contraindications. • Continuation of chronic β-blocker therapy is recommended unless the patient is in overt heart failure • Sublingual or intravenous nitrates are recommended to relieve angina; intravenous treatment is recommended in patients with recurrent angina, uncontrolled hypertension, or signs of heart failure. • In patients with suspected/confirmed vasospastic angina, calcium channel blockers, and nitrates should be considered and β-blockers avoided. <u>Recommendations for platelet inhibition in non-ST-elevation acute coronary syndromes</u> • Aspirin is recommended for all patients without contraindications at an initial oral loading dose of 150 to 300 mg (in aspirin-naïve patients) and a maintenance dose of 75 to 100 mg/day long-term regardless of treatment strategy. • A $P2Y_{12}$ inhibitor is recommended, in addition to aspirin, for 12 months unless there are contraindications such as excessive risks of bleeds. ○ Ticagrelor (180 mg loading dose, 90 mg twice daily) is recommended, in the absence of contraindication, for all patients at moderate-to-high risk of ischemic events (e.g., elevated cardiac troponins), regardless of initial treatment strategy and including those pretreated with clopidogrel (which should be discontinued when ticagrelor is started). ○ Prasugrel (60 mg loading dose, 10 mg daily dose) is recommended in patients who are proceeding to PCI if no contraindication. Prasugrel should be considered in preference to ticagrelor in NSTE-ACS patients who proceed to PCI. ○ Clopidogrel (300 to 600 mg loading dose, 75 mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel or who require oral anticoagulation. • $P2Y_{12}$ inhibitor administration for a shorter duration of three to six months after DES implantation may be considered in patients deemed at high bleeding risk. • Pre-treatment with a $P2Y_{12}$ inhibitor may be considered in patients with NSTE-ACS who are not planned to undergo an early invasive strategy. • It is not recommended to administer routine pre-treatment with a $P2Y_{12}$ inhibitor in patients in whom coronary anatomy is not known. • It is not recommended to administer prasugrel in patients whom coronary anatomy is not known. • GPIIb/IIIa inhibitors during PCI should be considered for bailout situations or thrombotic complications. • Cangrelor may be considered in $P2Y_{12}$ inhibitor-naïve patients undergoing PCI. • It is not recommended to administer GPIIb/IIIa inhibitors in patients whom coronary anatomy is not known. • $P2Y_{12}$ inhibitor administration in addition to aspirin beyond one year may be considered after careful assessment of the ischemic and bleeding risks of the patient. <u>Recommendations for anticoagulation in non-ST-elevation acute coronary syndromes</u> • Parenteral anticoagulation is recommended at the time of diagnosis according to both ischemic and bleeding risks.

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	• Fondaparinux is recommended as having the most favorable efficacy-safety profile regardless of the management strategy. • Bivalirudin is recommended as an alternative to UFH plus GPIIb/IIIa inhibitors during PCI. • UFH is recommended in patients undergoing PCI who did not receive any anticoagulant. • In patients on fondaparinux undergoing PCI, a single intravenous bolus of UFH is recommended during the procedure. • Enoxaparin or UFH are recommended when fondaparinux is not available. • Enoxaparin should be considered as an anticoagulant for PCI in patients pretreated for PCI with subcutaneous enoxaparin. • Additional activated clotting time-guided intravenous boluses of UFH during PCI may be considered following initial UFH treatment. • Discontinuation of anticoagulation should be considered after PCI, unless otherwise indicated. • Crossover between UFH and LMWH is not recommended. • In NSTEMI patients with no prior stroke/TIA and at high ischemic risk as well as low bleeding risk receiving aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily for approximately one year) may be considered after discontinuation of parenteral anticoagulation. <u>Recommendations for combining antiplatelet agents and anticoagulants in non-ST-elevation acute coronary syndrome patients requiring chronic oral anticoagulation</u> • In patients with a firm indication for oral anticoagulation (e.g., atrial fibrillation with a $CHADS_2$-VASc score ≥2, recent VTE, mechanical valve prosthesis), oral anticoagulation is recommended in addition to antiplatelet therapy. • An early invasive coronary angiography (within 24 hours) should be considered in moderate- to high-risk patients, irrespective of oral anticoagulant exposure, to expedite treatment allocation (medical vs PCI vs CABG) and to determine optimal antithrombotic regimen. • Initial dual antiplatelet therapy with aspirin plus a $P2Y_{12}$ inhibitor in addition to oral anticoagulation before coronary angiography is not recommended. • During PCI, additional parenteral anticoagulation is recommended, irrespective of the timing of the last dose of all non-vitamin K antagonist oral anticoagulants (NOACs) and if INR is <2.5 in VKA-treated patients. • Uninterrupted therapeutic anticoagulation with VKA or NOACs should be considered during the periprocedural phase. • Periprocedural DAPT administration consisting of aspirin and clopidogrel up to one week is recommended • Discontinuation of antiplatelet treatment in patients treated with an oral anticoagulant is recommended after 12 months • Following coronary stenting, dual (oral) antiplatelet therapy (DAPT) including new $P2Y_{12}$ inhibitors should be considered as an alternative to triple therapy for patients with non-ST-elevation acute coronary syndromes and atrial fibrillation with a $CHADS_2$-VASc score of 1 (in males) or 2 (in females). • If at low bleeding risk (HAS-BLED ≤2), triple therapy with oral anticoagulant, aspirin, and clopidogrel should be considered for six months, followed by oral anticoagulant and aspirin or clopidogrel continued up to 12 months. • If at high bleeding risk (HAS-BLED ≥3), triple therapy with oral anticoagulant, aspirin, and clopidogrel should be considered for one month, followed by oral anticoagulant and aspirin or clopidogrel continued up to 12 months irrespective of the stent type. • Dual therapy with oral anticoagulant and clopidogrel may be considered as an alternative to triple antithrombotic therapy in selected patients (HAS-BLED ≥3 and low risk of stent thrombosis).

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	• The use of ticagrelor or prasugrel as part of triple therapy is not recommended. • In medically managed patients, one antiplatelet agent in addition to oral anticoagulant should be considered for up to one year. <u>Recommendations for post-interventional and maintenance treatment</u> • In patients with NSTE-ACS with coronary stent implantation, DAPT with a $P2Y_{12}$ inhibitor on top of aspirin is recommended for 12 months unless there are contraindications such as excessive risk of bleeding. • Adding a second anti-thrombotic agent to aspirin for extended long-term secondary prevention should be considered in patients with a moderate to high risk of ischemic events and without increased risk of major bleeding. • After stent implantation with high risk of bleeding, discontinuation of $P2Y_{12}$ inhibitor therapy after three months should be considered • After stent implantation in patients undergoing DAPT, stopping aspirin after three to six months should be considered, depending on balance between ischemic and bleeding risk. • De-escalation of $P2Y_{12}$ inhibitor treatment may be considered as an alternative DAPT strategy, especially for ACS patients deemed unsuitable for potent platelet inhibition.
American College of Cardiology/ American Heart Association: **Guideline for the Management of ST-Elevation Myocardial Infarction (2013)**[18]	<u>Routine medical therapies: calcium channel blockers</u> • Evidence demonstrates that beneficial effect on infarct size or the rate of reinfarction when calcium channel blocker therapy was initiated during either the acute or convalescent phase of ST-segment elevation myocardial infarction (STEMI). However, calcium channel blockers may be useful to relieve ischemia, lower blood pressure, or control the ventricular response rate to atrial fibrillation in patients who are intolerant to β-blockers. • Use of immediate-release nifedipine is contraindicated in patients with STEMI due to hypotension and reflex sympathetic activation with tachycardia. <u>Routine medical therapies: β-blockers</u> • Oral β-blockers should be initiated within the first 24 hours in patients with an ST-segment elevation myocardial infarction (STEMI) who do not have any of the following: 1) signs of heart failure, 2) evidence of a low-output state, 3) increased risk of cardiogenic shock, 4) other contraindications to use of oral β-blockers (e.g., PR interval >24 seconds, second or third degree heart block, active asthma, reactive airway disease). • β-blockers should be continued during and after hospitalization for all patients with STEMI and with no contraindications to their use. • Patients with initial contraindications to the use of β-blockers in the first 24 hours after STEMI should be re-evaluated to determine their subsequent eligibility. • It is reasonable to administer intravenous β-blockers at the time of presentation to patients with STEMI and no contraindications to their use who are hypertensive or have ongoing ischemia. <u>Routine medical therapies: Renin-Angiotensin-Aldosterone System Inhibitors</u> • An angiotensin-converting enzyme (ACE) inhibitor should be administered within the first 24 hours to all patients with STEMI with anterior location, HF, or ejection fraction (EF) ≤40%, unless contraindicated. • An angiotensin receptor blocker (ARB) should be given to patients with STEMI who have indications for but are intolerant of ACE inhibitors. • An aldosterone antagonist should be given to patients with STEMI and no contraindications who are already receiving an ACE inhibitor and β-blocker and who have an EF ≤40% and either symptomatic heart failure or diabetes. <u>Routine medical therapies: Lipid management</u>

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	• High-intensity statin therapy should be initiated or continued in all patients with STEMI and no contraindications to its use. • It is reasonable to obtain a fasting lipid profile in patients with STEMI, preferably within 24 hours of presentation.
European Society of Cardiology: **Management of Acute Myocardial Infarction in Patients Presenting with ST-segment Elevation (2017)[19]**	Routine therapies in the acute, subacute and long term phase of ST-elevation myocardial infarction (STEMI) • Antiplatelet therapy with low dose aspirin (75 to 100 mg) is indicated indefinitely after STEMI. • Dual antiplatelet therapy with a combination of aspirin and prasugrel or aspirin and ticagrelor is recommended for 12 months after percutaneous coronary intervention (PCI), unless there are contraindications such as excessive risk of bleeding. • A proton pump inhibitor (PPI) in combination with dual antiplatelet therapy is recommended in patients at high risk of gastrointestinal bleeding. • In patients with an indication for oral anticoagulation, oral anticoagulants are indicated in addition to antiplatelet therapy. • In patients who are at high risk of severe bleeding complications, discontinuation of $P2Y_{12}$ inhibitor therapy after six months should be considered. • In STEMI patients with stent implantation and an indication for oral anticoagulation, triple therapy (oral anticoagulant, aspirin, and clopidogrel) should be considered for one to six months (according a balance between the estimated risk of recurrent coronary events and bleeding). • In patients with left ventricular thrombus, anticoagulation should be instituted for a minimum of six months, guided by repeated imaging. • In selected patients who receive aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily) may be considered if the patient is at low bleeding risk. • Dual antiplatelet therapy should be used up to one year in patients with STEMI who did not receive a stent unless there are contraindications such as excessive risk of bleeding. • In high ischemic-risk patients (age ≥50 years, and at least one of the following risk factors: age ≥65 years, diabetes mellitus on medication, prior spontaneous MAI, multivessel CAD, or chronic renal dysfunction with eGFR <60 mL/min) who have tolerated dual antiplatelet therapy without a bleeding complication, treatment with dual antiplatelet therapy in the form of ticagrelor 60 mg twice a day on top of aspirin for longer than 12 months may be considered for up to three years. • The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with aspirin and oral anticoagulation. • Oral treatment with β-blockers should be considered during hospital stay and continued thereafter in all patients without contraindications. • Oral treatment with β-blockers is indicated in patients with heart failure or left ventricular dysfunction, LVEF ≤40% unless contraindicated. • Intravenous β-blockers must be avoided in patients with hypotension or acute heart failure or AV block or severe bradycardia. • Intravenous β-blockers should be considered at the time of presentation in patients undergoing primary PCI without contraindications, with high blood pressure, tachycardia, and no signs of heart failure. • A fasting lipid profile must be obtained in all STEMI patients, as soon as possible after presentation. • It is recommended to initiate or continue high dose statins early after admission in all STEMI patients without contraindication or history of intolerance, regardless of initial cholesterol values and maintain it long-term. • An LDL-C goal of <1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline LDL-C is between 1.8 to 3.5 mmol/L (70 to 135 mg/dL) is recommended. • In patients with LDL-C >1.8 mmol/L (>70 mg/dL) despite a maximally tolerated statin dose who remain at high risk, further therapy to reduce LDL-C should be considered.

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	• ACE inhibitors are indicated starting within the first 24 hours of STEMI in patients with evidence of heart failure, LV systolic dysfunction, diabetes or an anterior infarct. • An ARB, preferably valsartan, is an alternative to ACE inhibitors in patients with heart failure or LV systolic dysfunction, particularly those who are intolerant to ACE inhibitors. • ACE inhibitors should be considered in all patients in the absence of contraindications. • Aldosterone antagonists, e.g. eplerenone, are indicated in patients with an ejection fraction ≤40% and heart failure or diabetes, provided no renal failure or hyperkalemia.
American College of Cardiology/ American Heart Association: **Guideline on the Primary Prevention of Cardiovascular Disease (2019)**[20]	<u>Top 10 messages for the primary prevention of cardiovascular disease</u> • The most important way to prevent atherosclerotic vascular disease, heart failure, and atrial fibrillation is to promote a healthy lifestyle throughout life. • A team-based care approach is an effective strategy for the prevention of cardiovascular disease. Clinicians should evaluate the social determinants of health that affect individuals to inform treatment decisions. • Adults who are 40 to 75 years of age and are being evaluated for cardiovascular disease prevention should undergo 10-year atherosclerotic cardiovascular disease (ASCVD) risk estimation and have a clinician–patient risk discussion before starting on pharmacological therapy, such as antihypertensive therapy, a statin, or aspirin. In addition, assessing for other risk-enhancing factors can help guide decisions about preventive interventions in select individuals, as can coronary artery calcium scanning. • All adults should consume a healthy diet that emphasizes the intake of vegetables, fruits, nuts, whole grains, lean vegetable or animal protein, and fish and minimizes the intake of trans fats, processed meats, refined carbohydrates, and sweetened beverages. For adults with overweight and obesity, counseling and caloric restriction are recommended for achieving and maintaining weight loss. • Adults should engage in at least 150 minutes per week of accumulated moderate-intensity physical activity or 75 minutes per week of vigorous-intensity physical activity. • For adults with type 2 diabetes mellitus, lifestyle changes, such as improving dietary habits and achieving exercise recommendations, are crucial. If medication is indicated, metformin is first-line therapy, followed by consideration of a sodium-glucose cotransporter 2 inhibitor or a glucagon-like peptide-1 receptor agonist. • All adults should be assessed at every healthcare visit for tobacco use, and those who use tobacco should be assisted and strongly advised to quit. • Aspirin should be used infrequently in the routine primary prevention of ASCVD because of lack of net benefit. • Statin therapy is first-line treatment for primary prevention of ASCVD in patients with elevated low-density lipoprotein cholesterol levels (≥190 mg/dL), those with diabetes mellitus, who are 40 to 75 years of age, and those determined to be at sufficient ASCVD risk after a clinician–patient risk discussion. • Nonpharmacological interventions are recommended for all adults with elevated blood pressure or hypertension. For those requiring pharmacological therapy, the target blood pressure should generally be <130/80 mm Hg. <u>Adults with Type 2 Diabetes Mellitus</u> • For all adults with T2DM, a tailored nutrition plan focusing on a heart-healthy dietary pattern is recommended to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors. • Adults with T2DM should perform at least 150 minutes per week of moderate-intensity physical activity or 75 minutes of vigorous-intensity physical activity to improve glycemic control, achieve weight loss if needed, and improve other

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	ASCVD risk factors. • For adults with T2DM, it is reasonable to initiate metformin as first-line therapy along with lifestyle therapies at the time of diagnosis to improve glycemic control and reduce ASCVD risk. • For adults with T2DM and additional ASCVD risk factors who require glucose-lowering therapy despite initial lifestyle modifications and metformin, it may be reasonable to initiate a sodium-glucose cotransporter 2 (SGLT-2) inhibitor or a glucagon-like peptide-1 receptor (GLP-1R) agonist to improve glycemic control and reduce CVD risk. <u>Adults with high blood cholesterol</u> • In adults at intermediate risk (≥7.5% to <20% 10-year ASCVD risk), statin therapy reduces risk of ASCVD, and in the context of a risk discussion, if a decision is made for statin therapy, a moderate-intensity statin should be recommended. • In intermediate risk (≥7.5% to <20% 10-year ASCVD risk) patients, LDL-C levels should be reduced by 30% or more, and for optimal ASCVD risk reduction, especially in patients at high risk (≥20% 10-year ASCVD risk), levels should be reduced by 50% or more. • In adults 40 to 75 years of age with diabetes, regardless of estimated 10-year ASCVD risk, moderate-intensity statin therapy is indicated. • In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL (≥4.9 mmol/L) or higher, maximally tolerated statin therapy is recommended. • In adults with diabetes mellitus who have multiple ASCVD risk factors, it is reasonable to prescribe high-intensity statin therapy with the aim to reduce LDL-C levels by 50% or more. • In intermediate-risk (≥7.5% to <20% 10-year ASCVD risk) adults, risk-enhancing factors favor initiation or intensification of statin therapy. • In intermediate-risk (≥7.5% to <20% 10-year ASCVD risk) adults or selected borderline-risk (5% to <7.5% 10-year ASCVD risk) adults in whom a coronary artery calcium score is measured for the purpose of making a treatment decision, AND o If the coronary artery calcium score is zero, it is reasonable to withhold statin therapy and reassess in five to 10 years, as long as higher-risk conditions are absent (e.g., diabetes, family history of premature CHD, cigarette smoking); o If coronary artery calcium score is one to 99, it is reasonable to initiate statin therapy for patients ≥55 years of age; o If coronary artery calcium score is 100 or higher or in the 75th percentile or higher, it is reasonable to initiate statin therapy. • In patients at borderline risk (5% to <7.5% 10-year ASCVD risk), in risk discussion, the presence of risk-enhancing factors may justify initiation of moderate-intensity statin therapy. <u>Adults with high blood pressure or hypertension</u> • In adults with elevated blood pressure (BP) or hypertension, including those requiring antihypertensive medications nonpharmacological interventions are recommended to reduce BP. These include: o weight loss; o a heart-healthy dietary pattern; o sodium reduction; o dietary potassium supplementation; o increased physical activity with a structured exercise program; and o limited alcohol. • In adults with an estimated 10-year ASCVD risk (ACC/AHA pooled cohort equations to estimate 10-year risk of ASCVD) of 10% or higher and an average

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	systolic BP (SBP) of 130 mm Hg or higher or an average diastolic BP (DBP) of 80 mm Hg or higher, use of BP-lowering medications is recommended for primary prevention of CVD. • In adults with confirmed hypertension and a 10-year ASCVD event risk of 10% or higher, a BP target of less than 130/80 mm Hg is recommended. • In adults with hypertension and chronic kidney disease, treatment to a BP goal of less than 130/80 mm Hg is recommended. • In adults with T2DM and hypertension, antihypertensive drug treatment should be initiated at a BP of 130/80 mm Hg or higher, with a treatment goal of less than 130/80 mm Hg. • In adults with an estimated 10-year ASCVD risk <10% and an SBP of 140 mm Hg or higher or a DBP of 90 mm Hg or higher, initiation and use of BP-lowering medication are recommended. • In adults with confirmed hypertension without additional markers of increased ASCVD risk, a BP target of less than 130/80 mm Hg may be reasonable. <u>Recommendations for treatment of tobacco use</u> • All adults should be assessed at every healthcare visit for tobacco use and their tobacco use status recorded as a vital sign to facilitate tobacco cessation. • To achieve tobacco abstinence, all adults who use tobacco should be firmly advised to quit. • In adults who use tobacco, a combination of behavioral interventions plus pharmacotherapy is recommended to maximize quit rates. • In adults who use tobacco, tobacco abstinence is recommended to reduce ASCVD risk. • To facilitate tobacco cessation, it is reasonable to dedicate trained staff to tobacco treatment in every healthcare system. • All adults and adolescents should avoid secondhand smoke exposure to reduce ASCVD risk. <u>Recommendations for aspirin use</u> • Low-dose aspirin (75 to 100 mg orally daily) might be considered for the primary prevention of ASCVD among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk. • Low-dose aspirin (75 to 100 mg orally daily) should not be administered on a routine basis for the primary prevention of ASCVD among adults >70 years of age. • Low-dose aspirin (75 to 100 mg orally daily) should not be administered for the primary prevention of ASCVD among adults of any age who are at increased risk of bleeding.
American Heart Association/American College of Cardiology/ Heart Failure Society of America: **2022 AHA/ACC /HFSA Guideline for the Management of Heart Failure (2022)**[21]	<u>Treatment of Stage A heart failure (HF)</u> • Hypertension should be controlled in accordance with guideline-directed medication therapy for hypertension to prevent symptomatic HF. (LoE: A) • In patients with type 2 diabetes and either established CVD or at high cardiovascular risk, SGLT-2 inhibitors should be used to prevent hospitalizations for HF. (LoE: A) • In the general population, healthy lifestyle habits such as regular physical activity, maintaining normal weight, healthy dietary patterns, and avoiding smoking are helpful to reduce future risk of HF. (LoE: B) • Patients at risk of developing HF, natriuretic peptide biomarker-based screening followed by team-based care, including a cardiovascular specialist optimizing therapy, can be useful to prevent the development of LV dysfunction (systolic or diastolic) or new-onset HF. (LoE: B) <u>Treatment of Stage B heart failure</u>

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	• In patients with LVEF≤40%, ACE inhibitors should be used to prevent HF and reduce mortality. (LoE: A) • In patients with a recent or remote history of MI or ACS, statins should be used to prevent symptomatic HF and adverse cardiovascular events. (LoE: A) • In patients with a recent MI and LVEF≤40% who are intolerant to ACE inhibitors, ARB should be used to prevent symptomatic HF and reduce mortality. (LoE: B) • In patients with a recent or remote history of MI or ACS and LVEF≤40%, evidence-based beta blockers should be used to reduce mortality. (LoE: B) • In patients who are at least 40 days post-MI with LVEF ≤30% and NYHA class I symptoms while receiving guideline-directed medication therapy and have reasonable expectation of meaningful survival for greater than one year, an implantable cardioverter-defibrillator is recommended for primary prevention of sudden cardiac death to reduce total mortality. (LoE: B) • In patients with LVEF ≤40%, beta blockers should be used to prevent symptomatic HF. (LoE: C) • In patients with LVEF ≤50%, thiazolidinediones should not be used because they increase the risk of HF, including hospitalizations. (LoE: B) • In patients with LVEF ≤50%, nondihydropyridine calcium channel blockers with negative inotropic effects may be harmful. (LoE: C) <u>Treatment for Stage C Heart Failure with Reduced Ejection Fraction (HfrEF)</u> • For patients with stage C HF, avoiding excessive sodium intake is reasonable to reduce congestive symptoms. (LoE: C) • In patients with HF who have fluid retention, diuretics are recommended to relieve congestion, improve symptoms, and prevent worsening HF. (LoE: B) • For patients with HF and congestive symptoms, addition of a thiazide (e.g., metolazone) to treatment with a loop diuretic should be reserved for patients who do not respond to moderate or high dose loop diuretics to minimize electrolyte abnormalities. (LoE: B) • In patients with HfrEF and NYHA class II to III symptoms, the use of an ARNI is recommended to reduce morbidity and mortality. (LoE: A) • In patients with previous or current symptoms of chronic HfrEF, the use of an ACE inhibitor is beneficial to reduce morbidity and mortality when the use of an ARNI is not feasible. (LoE: A) • In patients with previous or current symptoms of chronic HfrEF, who are intolerant to an ACE inhibitor because of cough or angioedema, and when the use of an ARNI is not feasible, the use of an ARB is recommended to reduce morbidity and mortality. (LoE: A) • In patients with chronic symptomatic HfrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality. (LoE: B) • ARNIs should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor. (LoE: B) • ARNI or ACE inhibitors should not be administered in patients with a history of angioedema. (LoE: C) • In patients with HfrEF, with current or previous symptoms, use of one of the three β-blockers proven to reduce mortality (e.g., bisoprolol, carvedilol, sustained-release metoprolol succinate) is recommended to reduce mortality and hospitalizations. (LoE: A) • In patients with HfrEF and NYHA class II to IV symptoms, a mineralocorticoid receptor antagonist (spironolactone or eplerenone) is recommended to reduce morbidity and mortality, if eGFR is >30 mL/min/1.73 m^2 and serum potassium is <5.0 mEq/L. Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely followed thereafter to minimize risk of hyperkalemia and renal insufficiency. (LoE: A)

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	• In patients taking a mineralocorticoid receptor antagonist whose serum potassium cannot be maintained at <5.5 mEq/L, mineralocorticoid receptor antagonist should be discontinued to avoid life threatening hyperkalemia. (LoE: B) • In patients with symptomatic chronic HfrEF, SGLT-2 an inhibitor is recommended to reduce hospitalization for HF and cardiovascular mortality, irrespective of the presence of type 2 diabetes. (LoE: A) • The combination of hydralazine and isosorbide dinitrate is recommended to improve symptoms and reduce morbidity and mortality for patients self-identified as African Americans with NYHA class III to IV HfrEF receiving optimal therapy. (LoE: A) • In patients with current or previous symptomatic HfrEF who cannot be given first-line agents, such as an ARNI, ACE inhibitor or ARB because of drug intolerance or renal insufficiency, a combination of hydralazine and isosorbide dinitrate might be considered to reduce morbidity and mortality. (LoE: C) • In patients with HF class II to IV symptoms, omega-3 polyunsaturated fatty acid supplementation may be reasonable to use as adjunctive therapy to reduce mortality and cardiovascular hospitalizations. (LoE: B) • In patients with chronic HfrEF without specific indication (e.g., venous thromboembolism, atrial fibrillation, a previous thromboembolic event, or a cardioembolic source, anticoagulation is not recommended. (LoE: B) • Dihydropyridine and non-dihydropyridine calcium channel blockers are not recommended for patients with HfrEF. (LoE: A) • In patients with HfrEF, vitamins, nutritional supplements, and hormonal therapy are not recommended other than to correct specific deficiencies. (LoE: B) • In patients with HfrEF, class IC antiarrhythmic medication and dronedarone may increase risk of mortality. (LoE: A) • In patients with HfrEF, thiazolidinediones increase the risk of worsening HF symptoms and hospitalizations. (LoE: A) • In patients with type 2 diabetes and high cardiovascular risk, the DPP-4 inhibitors, saxagliptin and alogliptin, increase the risk of HF hospitalization and should be avoided in patients with HF. (LoE: B) • In patients with HfrEF, nonsteroidal anti-inflammatory drugs worsen HF symptoms and should be avoided or withdrawn whenever possible. (LoE: B) • For patients with symptomatic (NYHA class II to III) stable chronic HfrEF (LVEF ≤35%) who are receiving guideline-directed medical therapy, including a maximally tolerated dose of a beta blocker, and who are in sinus rhythm with a heart rate of ≥70 beats per minute at rest, ivabradine can be beneficial to reduce HF hospitalizations and cardiovascular death. (LoE: B) • In patients with symptomatic HfrEF despite guideline-directed medical therapy or who are unable to tolerate guideline-directed medical therapy, digoxin might be considered to decrease hospitalizations for HF. (LoE: B) • In select high-risk patients with HfrEF and recent worsening of HF already on guideline-directed medical therapy, an oral soluble guanylate cyclase stimulator (vericiguat) may be considered to reduce HF hospitalization and cardiovascular death. (LoE: B) <u>Pharmacological treatment for Stage C HF with mildly reduced EF and improved EF</u> • In patients with HF with mildly reduced EF, SGLT-2 inhibitors can be beneficial in decreasing HF hospitalizations and cardiovascular mortality. (LoE: B) • Among patients with current or previous symptomatic HF with mildly reduced EF (LVEF, 41 to 49%), use of evidence-based beta blockers for HfrEF, ARNI, ACE inhibitor or ARB, and mineralocorticoid receptor antagonists may be considered to reduce the risk of HF hospitalization and cardiovascular mortality, particularly among patients with LVEF on the lower end of this spectrum. (LoE: B) • In patients with HF with improved EF after treatment, guideline-directed medical

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	therapy should be continued to prevent relapse of HF and LV dysfunction, even in patients who may become asymptomatic. (LoE: B) <u>Pharmacological treatment for Stage C HF with preserved EF (HfpEF)</u> • Patients with hypertension and HfpEF should have medication titrated to attain blood pressure targets in accordance with published clinical practice guidelines to prevent morbidity. (LoE: C) • SGLT-2 inhibitors can be beneficial in decreasing HF hospitalizations and cardiovascular mortality. (LoE: B) • In patients with HfpEF, the use of a mineralocorticoid receptor antagonist, ARB, or ARNI may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum. (LoE: B) • Routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or quality of life in patients with HfpEF is ineffective. (LoE: B) <u>Treatment of Stage D (advanced/refractory) HF</u> • For patients with advanced HF and hyponatremia, the benefit of fluid restriction to reduce congestive symptoms is uncertain. (LoE: C) • Continuous intravenous inotropic support is reasonable as "bridge therapy" in patients with HF (Stage D) refractory to guideline-directed medical therapy and device therapy who are eligible for and awaiting mechanical circulatory support or cardiac transplantation. (LoE: B) • In select patients with HF Stage D, despite optimal guideline-directed medical therapy and device therapy who are ineligible for either mechanical circulatory support or cardiac transplantation, continuous intravenous inotropic support may be considered as palliative therapy for symptom control and improvement in functional status. (LoE: B) • Long-term use of either continuous or intermittent, intravenous inotropic agents, for reasons other than palliative care or as a bridge to advanced therapies, is potentially harmful. (LoE: B)
European Society of Cardiology: **Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (2021)**[22]	<u>Pharmacological treatments indicated in patients with (NYHA Class II-IV) heart failure with reduced ejection fraction</u> • An ACE inhibitor is recommended, in addition to a β-blocker, for symptomatic patients with HfrEF to reduce the risk of HF hospitalization and death. • A mineralocorticoid receptor antagonist (MRA) is recommended for patients with HfrEF, who remain symptomatic despite treatment with an ACE inhibitor and a β-blocker, to reduce the risk of HF hospitalization and death. • Dapagliflozin or empagliflozin are recommended for patients with HfrEF to reduce the risk of HF hospitalization and death. Dapagliflozin or empagliflozin are recommended, in addition to optimal medical therapy with an ACE-I/ARNI, a β-blocker and an MRA, for patients with HfrEF regardless of diabetes status. • Sacubitril-valsartan is recommended as a replacement for an ACE inhibitor to further reduce the risk of HF hospitalization and death in ambulatory patients with HfrEF who remain symptomatic despite optimal treatment with an ACE inhibitor, a β-blocker, and a mineralocorticoid receptor antagonist. • Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion. • Ivabradine should be considered to reduce the risk of HF hospitalization or cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm despite treatment with an evidence-based dose of β-blocker (or maximum tolerated dose below that), ACE inhibitor (or ARB), and a mineralocorticoid receptor antagonist (or ARB). • Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm who are unable to tolerate or have

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	contraindications for a β-blocker. Patients should also receive an ACE inhibitor (or ARB) and a mineralocorticoid receptor antagonist (or ARB). • An ARB is recommended to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients unable to tolerate an ACE inhibitor (patients should also receive a β-blocker and mineralocorticoid receptor antagonist). • An ARB may be considered to reduce the risk of HF hospitalization and death in patients who are symptomatic despite treatment with a β-blocker who are unable to tolerate a mineralocorticoid receptor antagonist. • Vericiguat may be considered in patients in NYHA class II-IV who have had worsening HF despite treatment with an ACE-I (or ARNI), a β-blocker and an MRA to reduce the risk of CV mortality or HF hospitalization. • Hydralazine and isosorbide dinitrate should be considered in self-identified black patients with LVEF ≤35% or with an LVEF <45% combined with a dilated LV in NYHA Class III–IV despite treatment with an ACE-I a β-blocker and a mineralocorticoid receptor antagonist to reduce the risk of HF hospitalization and death. • Hydralazine and isosorbide dinitrate may be considered in symptomatic patients with HfrEF who can tolerate neither an ACE inhibitor nor an ARB (or they are contraindicated) to reduce the risk of death. • Digoxin is a treatment with less-certain benefits and may be considered in symptomatic patients in sinus rhythm despite treatment with an ACE inhibitor (or ARB), a β-blocker and a mineralocorticoid receptor antagonist, to reduce the risk of hospitalization (both all-cause and HF-hospitalizations). <u>Recommendations for treatment of patients with (NYHA class II-IV) heart failure with mildly reduced ejection fraction (HfmrEF)</u> • Diuretics are recommended in patients with congestion and HfmrEF in order to alleviate symptoms and signs. • An ACE inhibitor may be considered for patients with HfmrEF to reduce the risk of HF hospitalization and death. • An ARB may be considered for patients with HfmrEF to reduce the risk of HF hospitalization and death. • A β-blocker may be considered for patients with HfmrEF to reduce the risk of HF hospitalization and death. • An MRA may be considered for patients with HfmrEF to reduce the risk of HF hospitalization and death. • Sacubitril/valsartan may be considered for patients with HfmrEF to reduce the risk of HF hospitalization and death. <u>Recommendations for treatment of patients with heart failure with preserved ejection fraction (HfpEF)</u> • It is recommended to screen patients with HfpEF for both cardiovascular and noncardiovascular comorbidities, which, if present, should be treated provided safe and effective interventions exist to improve symptoms, well-being and/or prognosis. • Diuretics are recommended in congested patients with HfpEF in order to alleviate symptoms and signs. <u>Recommendations for the primary prevention of heart failure in patients with risk factors for its development</u> • Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life. • Treatment with statins is recommended in patients at high risk of CV disease or with CV disease in order to prevent or delay the onset of HF, and to prevent HF

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	hospitalizations. • SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with diabetes at high risk of CV disease or with CV disease in order to prevent HF hospitalizations. • Counselling against sedentary habit, obesity, cigarette smoking, and alcohol abuse is recommended to prevent or delay the onset of HF. <u>Recommendations for the initial management of patients with acute heart failure – pharmacotherapy</u> • Intravenous loop diuretics are recommended for all patients with acute HF admitted with signs/symptoms of fluid overload to improve symptoms. It is recommended to regularly monitor symptoms, urine output, renal function and electrolytes during use of intravenous diuretics. • Combination of a loop diuretic with thiazide type diuretic should be considered in patients with resistant oedema who do not respond to an increase in loop diuretic doses. • In patients with acute HF and SBP >110 mmHg, intravenous vasodilators may be considered as initial therapy to improve symptoms and reduce congestion. • Inotropic agents may be considered in patients with SBP <90 mmHg and evidence of hypoperfusion who do not respond to standard treatment, including fluid challenge, to improve peripheral perfusion and maintain end-organ function. • Inotropic agents are not recommended routinely, due to safety concerns, unless the patient has symptomatic hypotension and evidence of hypoperfusion. • A vasopressor, preferably norepinephrine, may be considered in patients with cardiogenic shock to increase blood pressure and vital organ perfusion. • Thromboembolism prophylaxis (e.g., with LMWH) is recommended in patients not already anticoagulated and with no contraindication to anticoagulation, to reduce the risk of deep venous thrombosis and pulmonary embolism. • Routine use of opiates is not recommended, unless in selected patients with severe/intractable pain or anxiety.
American Heart Association/ American College of Cardiology/ Heart Rhythm Society: **2023 ACC/AHA/ACCP/ HRS Guideline for the Diagnosis and Management of Atrial Fibrillation (2023)**[23]	<u>Top 10 Take-Home Messages</u> • Stages of atrial fibrillation (AF): The previous classification of AF, which was based only on arrhythmia duration, although useful, tended to emphasize therapeutic interventions. The new proposed classification, using stages, recognizes AF as a disease continuum that requires a variety of strategies at the different stages, from prevention, lifestyle and risk factor modification, screening, and therapy. • AF risk factor modification and prevention: This guideline recognizes lifestyle and risk factor modification as a pillar of AF management to prevent onset, progression, and adverse outcomes. The guideline emphasizes risk factor management throughout the disease continuum and offers more prescriptive recommendations, accordingly, including management of obesity, weight loss, physical activity, smoking cessation, alcohol moderation, hypertension, and other comorbidities. • Flexibility in using clinical risk scores and expanding beyond CHA2DS2-VASc for prediction of stroke and systemic embolism: Recommendations for anticoagulation are now made based on yearly thromboembolic event risk using a validated clinical risk score, such as CHA2DS2-VASc. However, patients at an intermediate annual risk score who remain uncertain about the benefit of anticoagulation can benefit from consideration of other risk variables to help inform the decision, or the use of other clinical risk scores to improve prediction, facilitate shared decision making, and incorporate into the electronic medical record. • Consideration of stroke risk modifiers: Patients with AF at intermediate to low (<2%) annual risk of ischemic stroke can benefit from consideration of factors that might modify their risk of stroke, such as the characteristics of their AF (e.g.,

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	burden), nonmodifiable risk factors (sex), and other dynamic or modifiable factors (blood pressure control) that may inform shared decision-making discussions. • Early rhythm control: With the emergence of new and consistent evidence, this guideline emphasizes the importance of early and continued management of patients with AF that should focus on maintaining sinus rhythm and minimizing AF burden. • Catheter ablation of AF receives a Class 1 indication as first-line therapy in selected patients: Recent randomized studies have demonstrated the superiority of catheter ablation over drug therapy for rhythm control in appropriately selected patients. In view of the most recent evidence, we upgraded the Class of Recommendation. • Catheter ablation of AF in appropriate patients with heart failure with reduced ejection fraction receives a Class 1 indication: Recent randomized studies have demonstrated the superiority of catheter ablation over drug therapy for rhythm control in patients with heart failure and reduced ejection failure. In view of the data, we upgraded the Class of Recommendation for this population of patients. • Recommendations have been updated for device-detected AF: In view of recent studies, more prescriptive recommendations are provided for patients with device-detected AF that consider the interaction between episode duration and the patient's underlying risk for thromboembolism. This includes considerations for patients with AF detected via implantable devices and wearables. • Left atrial appendage occlusion devices receive higher level Class of Recommendation: In view of additional data on safety and efficacy of left atrial appendage occlusion devices, the Class of Recommendation has been upgraded to 2a compared with the 2019 AF Focused Update for use of these devices in patients with long-term contraindications to anticoagulation. • Recommendations are made for patients with AF identified during medical illness or surgery (precipitants): Emphasis is made on the risk of recurrent AF after AF is discovered during noncardiac illness or other precipitants, such as surgery. <u>Prevention of Thromboembolism</u> • Recommendations for Antithrombotic Therapy ○ For patients with atrial fibrillation (AF) and an estimated annual thromboembolic risk of ≥2% per year (e.g., CHA2DS2-VASc score of ≥2 in men and ≥3 in women), anticoagulation is recommended to prevent stroke and systemic thromboembolism. ○ In patients with AF who do not have a history of moderate to severe rheumatic mitral stenosis or a mechanical heart valve, and who are candidates for anticoagulation, direct oral anticoagulants (DOACs) are recommended over warfarin to reduce the risk of mortality, stroke, systemic embolism, and intracranial hemorrhage (ICH). ○ For patients with AF and an estimated annual thromboembolic risk of ≥1% but <2% per year (equivalent to CHA2DS2-VASc score of 1 in men and 2 in women), anticoagulation is reasonable to prevent stroke and systemic thromboembolism. ○ In patients with AF who are candidates for anticoagulation and without an indication for antiplatelet therapy, aspirin either alone or in combination with clopidogrel as an alternative to anticoagulation is not recommended to reduce stroke risk. ○ In patients with AF without risk factors for stroke, aspirin monotherapy for prevention of thromboembolic events is of no benefit. • Considerations in Managing Anticoagulants ○ For patients with AF receiving DOACs, optimal management of drug interactions is recommended for those receiving concomitant therapy with interacting drugs, especially CYP3A4 and/or p-glycoprotein inhibitors or inducers.

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	○ For patients with AF receiving warfarin, (excludes patients with mechanical valves) a target INR between 2 and 3 is recommended, as well as optimal management of drug-drug interactions, consistency in vitamin K dietary intake, and routine INR monitoring to improve time in therapeutic range and to minimize risks of preventable thromboembolism or major bleeding. ○ For patients with AF, nonevidence-based doses of DOACs should be avoided to minimize risks of preventable thromboembolism or major bleeding and to improve survival. • Recommendations for AF Complicating acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) ○ In patients with AF and an increased risk for stroke who undergo PCI, DOACs are preferred over vitamin K antagonists (VKAs) in combination with antiplatelet therapy (APT) to reduce the risk of clinically relevant bleeding. ○ In most patients with AF who take oral anticoagulation and undergo PCI, early discontinuation of aspirin (one to four weeks) and continuation of dual antithrombotic therapy with oral anticoagulant (OAC) and a P2Y12 inhibitor is preferred over triple therapy (OAC, P2Y12 inhibitor, and aspirin) to reduce the risk of clinically relevant bleeding. • Recommendation for Chronic Coronary Disease (CCD) ○ In patients with AF and CCD (beyond one year after revascularization or coronary artery disease (CAD) not requiring coronary revascularization) without history of stent thrombosis, oral anticoagulation monotherapy is recommended over the combination therapy of OAC and single APT (aspirin or P2Y12 inhibitor) to decrease the risk of major bleeding. • Recommendation for Peripheral Artery Disease (PAD) ○ In patients with AF and concomitant stable PAD, monotherapy oral anticoagulation is reasonable over dual therapy (anticoagulation plus aspirin or P2Y12 inhibitors) to reduce the risk of bleeding. • Recommendations for Chronic Kidney Disease (CKD)/Kidney Failure ○ For patients with AF at elevated risk for stroke and CKD stage 3, treatment with warfarin or, preferably, evidence-based doses of direct thrombin or factor Xa inhibitors is recommended to reduce the risk of stroke. ○ For patients with AF at elevated risk for stroke and CKD stage 4, treatment with warfarin or labeled doses of DOACs is reasonable to reduce the risk of stroke. ○ For patients with AF at elevated risk for stroke and who have end-stage CKD (CrCl <15 mL/min) or are on dialysis, it might be reasonable to prescribe warfarin (INR 2.0 to 3.0) or an evidence-based dose of apixaban for oral anticoagulation to reduce the risk of stroke. • Recommendations for AF in valvular heart disease (VHD) ○ In patients with rheumatic mitral stenosis or mitral stenosis of moderate or greater severity and history of AF, long-term anticoagulation with warfarin is recommended over DOACs, independent of the CHA2DS2-VASc score to prevent cardiovascular events, including stroke or death. ○ In patients with AF and valve disease other than moderate or greater mitral stenosis or a mechanical heart valve, DOACs are recommended over VKAs. <u>Rate control</u> • Broad Considerations for Rate Control ○ In patients with AF, shared decision-making with the patient is recommended to discuss rhythm- versus rate-control strategies (taking into consideration clinical presentation, comorbidity burden, medication profile, and patient preferences), discuss therapeutic options, and for assessing long-term benefits. ○ In patients with AF without HF who are candidates for select rate-control strategies, heart rate target should be guided by underlying patient symptoms, in general aiming at a resting heart rate of <100 to 110 bpm.

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	• Recommendations for Acute Rate Control ○ In patients with AF with rapid ventricular response who are hemodynamically stable, beta blockers or nondihydropyridine calcium channel blockers (verapamil, diltiazem; provided that EF >40%) are recommended for acute rate control. ○ In patients with AF with rapid ventricular response in whom beta blockers and nondihydropyridine calcium channel blockers are ineffective or contraindicated, digoxin can be considered for acute rate control, either alone or in combination with the aforementioned agents. ○ In patients with AF with rapid ventricular response, the addition of intravenous magnesium to standard rate-control measures is reasonable to achieve and maintain rate control. ○ In patients with AF with rapid ventricular response who are critically ill and/or in decompensated HF in whom beta blockers and nondihydropyridine calcium channel blockers are ineffective or contraindicated, intravenous amiodarone may be considered for acute rate control. Consider the risk of cardioversion and stroke when using amiodarone as a rate-control agent. ○ In patients with AF with rapid ventricular response and known moderate or severe LV systolic dysfunction with or without decompensated HF, intravenous nondihydropyridine calcium channel blockers should not be administered. • Recommendations for Long-Term Rate Control ○ In patients with AF, beta blockers or nondihydropyridine calcium channel blockers (diltiazem, verapamil) are recommended for long-term rate control with the choice of agent according to underlying substrate and comorbid conditions. ○ For patients with AF in whom measuring serum digoxin levels is indicated, it is reasonable to target levels <1.2 ng/mL. ○ In patients with AF and HF symptoms, digoxin is reasonable for long-term rate control in combination with other rate-controlling agents, or as monotherapy if other agents are not preferred, not tolerated, or contraindicated. ○ In patients with AF and LVEF <40%, nondihydropyridine calcium channel–blocking drugs should not be administered given their potential to exacerbate HF. ○ In patients with permanent AF who have risk factors for cardiovascular events, dronedarone should not be used for long-term rate control. <u>Rhythm Control</u> • Recommendations for Pharmacological Cardioversion ○ For patients with AF, pharmacological cardioversion is reasonable as an alternative to electrical cardioversion for those who are hemodynamically stable or in situations when electrical cardioversion is preferred but cannot be performed. ○ For patients with AF, ibutilide is reasonable for pharmacological cardioversion for patients without depressed LV function (LVEF <40%). ○ For patients with AF, intravenous amiodarone is reasonable for pharmacological cardioversion, although time to conversion is generally longer than with other agents (8-12 hours). ○ For patients with recurrent AF occurring outside the setting of a hospital, the “pill-in-the-pocket” (PITP) approach with a single oral dose of flecainide or propafenone, with a concomitant atrioventricular nodal blocking agent, is reasonable for pharmacological cardioversion if previously tested in a monitored setting. ○ For patients with AF, use of intravenous procainamide may be considered for pharmacological cardioversion when other intravenous agents are contraindicated or not preferred.

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	• Recommendations for Specific Drug Therapy for Long-Term Maintenance of Sinus Rhythm ○ For patients with AF and HfrEF (≤40%), therapy with dofetilide or amiodarone is reasonable for long-term maintenance of sinus rhythm. ○ For patients with AF and no previous MI, or known or suspected significant structural heart disease, or ventricular scar or fibrosis, use of flecainide or propafenone is reasonable for long-term maintenance of sinus rhythm. ○ For patients with AF without recent decompensated HF or severe LV dysfunction, use of dronedarone is reasonable for long-term maintenance of sinus rhythm. ○ For patients with AF without significant baseline QT interval prolongation or uncorrected hypokalemia or hypomagnesemia, use of dofetilide is reasonable for long-term maintenance of sinus rhythm, with proper dose selection based on kidney function and close monitoring of the QT interval, serum potassium and magnesium concentrations, and kidney function. ○ For patients with AF and normal LV function, use of low-dose amiodarone (100 to 200 mg/d) is reasonable for long-term maintenance of sinus rhythm but, in view of its adverse effect profile, should be reserved for patients in whom other rhythm control strategies are ineffective, not preferred, or contraindicated. ○ For patients with AF without significant baseline QT interval prolongation, hypokalemia, hypomagnesemia, or bradycardia, use of sotalol may be considered for long-term maintenance of sinus rhythm, with proper dose selection based on kidney function and close monitoring of the QT interval, heart rate, serum potassium and magnesium concentrations, and kidney function. ○ In patients with previous MI and/or significant structural heart disease, including HfrEF (LVEF ≤40%), flecainide and propafenone should not be administered due to the risk of worsening HF, potential proarrhythmia, and increased mortality. ○ For patients with AF, dronedarone should not be administered for maintenance of sinus rhythm to those with NYHA class III and IV HF or patients who have had an episode of decompensated HF in the past 4 weeks, due to the risk of increased early mortality associated with worsening HF. <u>Management of Patients With HF</u> • Recommendations for Management of AF in Patients With HF ○ In patients who present with a new diagnosis of HfrEF and AF, arrhythmia-induced cardiomyopathy should be suspected, and an early and aggressive approach to AF rhythm control is recommended. ○ In appropriate patients with AF and HfrEF who are on guideline-directed management and therapy, and with reasonable expectation of procedural benefit, catheter ablation is beneficial to improve symptoms, quality of life, ventricular function, and cardiovascular outcomes. ○ In appropriate patients with symptomatic AF and HfpEF with reasonable expectation of benefit, catheter ablation can be useful to improve symptoms and improve quality of life. ○ In patients with AF and HF, digoxin is reasonable for rate control, in combination with other rate-controlling agents or as monotherapy if other agents are not tolerated. ○ In patients with AF and HF with rapid ventricular rates in whom beta blockers or calcium channel blockers are contraindicated or ineffective, intravenous amiodarone is reasonable for acute rate control. ○ In patients with AF, HfrEF (LVEF <50%), and refractory rapid ventricular response who are not candidates for or in whom rhythm control has failed, atrioventricular nodal ablation (AVNA) and biventricular pacing therapy can

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	be useful to improve symptoms, quality of life, and EF. ○ In patients with AF, HF, and implanted biventricular pacing therapy in whom an effective pacing percentage cannot be achieved with pharmacological therapy, AVNA can be beneficial to improve functional class, reduce the risk of ICD shock, and improve survival. ○ In patients with AF-induced cardiomyopathy who have recovered LV function, long-term surveillance can be beneficial to detect recurrent AF in view of the high risk of recurrence of arrhythmia-induced cardiomyopathy. ○ In patients with suspected AF-induced cardiomyopathy or refractory HF symptoms undergoing pharmacological rate-control therapy for AF, a stricter rate-control strategy (target heart rate <80 bpm at rest and <110 bpm during moderate exercise) may be reasonable. ○ In patients with AF and HfrEF who undergo AVNA, conduction system pacing of the His bundle or left bundle branch area may be reasonable as an alternative to biventricular pacing to improve symptoms, quality of life, and LV function. ○ In patients with AF and known LVEF <40%, nondihydropyridine calcium channel–blocking drugs should not be administered because of their potential to exacerbate HF. ○ For patients with AF, dronedarone should not be administered for maintenance of sinus rhythm to those with NYHA class III and IV HF or patients who have had an episode of decompensated HF in the past four weeks, due to the risk of increased early mortality associated with worsening HF.
National Institute for Health and Care Excellence: **Atrial Fibrillation: Diagnosis and Management (2021)**[24]	Rate control • Offer rate control as the first-line treatment strategy for atrial fibrillation except in people: ○ whose atrial fibrillation has a reversible cause ○ who have heart failure thought to be primarily caused by atrial fibrillation ○ with new-onset atrial fibrillation ○ with atrial flutter whose condition is considered suitable for an ablation strategy to restore sinus rhythm ○ for whom a rhythm-control strategy would be more suitable based on clinical judgement. • Offer either a standard β-blocker (that is, a β-blocker other than sotalol) or a rate-limiting calcium channel blocker (CCB) (diltiazem or verapamil) as initial monotherapy to people with atrial fibrillation (AF) unless the person has the features described above. Base the choice of drug on the person's symptoms, heart rate, comorbidities and preferences.. • Consider digoxin monotherapy for initial rate control for people with non-paroxysmal atrial fibrillation if the person does no or very little physical exercise or if other rate-limiting drug options are ruled out because of comorbidities or the person's preferences.. • If monotherapy does not control symptoms, and if continuing symptoms are thought to be due to poor ventricular rate control, consider combination therapy with any two of the following: a β-blocker, diltiazem, and digoxin. • Do not offer amiodarone for long-term rate control. Rhythm control • Consider pharmacological and/or electrical rhythm control for people with AF whose symptoms continue after heart rate has been controlled or for whom a rate-control strategy has not been successful. Drug treatment for long-term rhythm control • Assess the need for drug treatment for long-term rhythm control, taking into account the person's preferences, associated comorbidities, risks of treatment, and

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	likelihood of recurrence of AF. • Do not offer class 1c antiarrhythmic drugs such as flecainide or propafenone to people with known ischaemic or structural heart disease. • If drug treatment for long-term rhythm control is needed, consider a standard β-blocker as first-line treatment unless there are contraindications. • If β-blockers are contraindicated or unsuccessful, assess the suitability of alternative drugs for rhythm control, taking comorbidities into account. • Dronedarone is recommended as an option for the maintenance of sinus rhythm after successful cardioversion in people with paroxysmal or persistent atrial fibrillation: o Whose AF is not controlled by first-line therapy (usually including β-blockers), that is, as a second-line treatment option and after alternative options have been considered AND o Who have at least one of the following cardiovascular risk factors: ▪ Hypertension requiring drugs of at least two different classes. ▪ Diabetes mellitus. ▪ Previous TIA, stroke, or systemic embolism. ▪ Left atrial diameter of 50 mm or greater, OR ▪ Age ≥70 years, AND o Who do not have left ventricular systolic dysfunction, AND o Who do not have a history of, or current, heart failure. • People who do not meet the criteria above who are currently receiving dronedarone should have the option to continue treatment until they and their clinicians consider it appropriate to stop. • Consider amiodarone for people with left ventricular impairment or heart failure. • Do not offer class 1c antiarrhythmic drugs such as flecainide or propafenone to people with known ischemic or structural heart disease. • Where people have infrequent paroxysms and few symptoms, or where symptoms are induced by known precipitants (such as alcohol, caffeine), a 'no drug treatment' strategy or a 'pill-in-the-pocket' strategy should be considered and discussed with the person. <u>Preventing postoperative atrial fibrillation</u> • In people having cardiothoracic surgery: o reduce the risk of postoperative atrial fibrillation by offering one of the following: amiodarone; a standard β-blocker (that is, a β-blocker other than sotalol); a rate-limiting calcium-channel blocker (diltiazem or verapamil) o do not offer digoxin. • In people having cardiothoracic surgery who are already on β-blocker therapy, continue this treatment unless contraindications develop (such as postoperative bradycardia or hypotension). • Do not start statins in people having cardiothoracic surgery solely to prevent postoperative atrial fibrillation. • In people having cardiothoracic surgery who are already on statins, continue this treatment. For further advice on statins for the prevention of cardiovascular disease, see NICE's guideline on cardiovascular disease: risk assessment and reduction.
American Association for Thoracic Surgery: **2014 AATS Guidelines for the Prevention and Management of Peri-Operative**	<u>Recommended prevention strategies for all postoperative atrial fibrillation (POAF) patients</u> • Patients taking β-blockers prior to thoracic surgery should continue them in the postoperative period to avoid β-blockade withdrawal. • Intravenous magnesium supplementation may be considered to prevent postoperative AF when serum magnesium level is low or it is suspected that total body magnesium is depleted. • Digoxin should not be used for prophylaxis against AF.

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Atrial Fibrillation and Flutter (POAF) for Thoracic Surgical Procedures (2014)[25]	<u>Recommended prevention strategies for intermediate to high-risk POAF patients</u> • It is reasonable to administer diltiazem to those patients with preserved cardiac function who are not taking β-blockers preoperatively in order to prevent POAF. • It is reasonable to consider the postoperative administration of amiodarone to reduce the incidence of POAF for intermediate and high risk patients undergoing pulmonary resection. • Postoperative administration of intravenous amiodarone may be considered to prevent POAF in patients undergoing esophagectomy. • Atorvastatin may be considered to prevent POAF for statin naïve patients scheduled for intermediate and high risk thoracic surgical procedures. <u>Rate control recommendations for patients with new onset POAF</u> • Intravenous administration of β-blockers (e.g., esmolol or metoprolol) or nondihydropyridine calcium channel blockers (diltiazem or verapamil) is recommended to achieve rate control (heart rate ≤110 bpm) for patients who develop POAF with rapid ventricular response. • Caution should be used with patients with hypotension, left ventricular (LV) dysfunction, or heart failure. • Combination use of atrioventricular (AV) nodal blocking agents, such as β-blockers (e.g., esmolol or metoprolol), nondihydropyridine calcium channel antagonists (e.g., diltiazem or verapamil), or digoxin, can be useful to control heart rates when a single agent fails to control rates of POAF. The choice should be individualized and doses modified to avoid bradycardia. • For patients with hypotension, heart failure or LV dysfunction, or when other measures are unsuccessful or contraindicated, intravenous amiodarone can be useful for control of heart rate. Amiodarone could result in conversion to sinus rhythm, and if it is initiated after 48 hours of AF, both a transesophageal echocardiography (TEE) when possible, to rule out left atrial/LA appendage (LA/LAA) thrombus, and full anticoagulation should be considered. • For patients with heart failure, LV dysfunction or hypotension, intravenous digoxin may be considered for rate control of POAF. • For patients with ventricular preexcitation (i.e., Wolff-Parkinson-White syndrome) and POAF, use of AV nodal blocking agents, such as β-blockers (e.g., esmolol or metoprolol), intravenous amiodarone, nondihydropyridine calcium channel antagonists (e.g., diltiazem or verapamil), or digoxin, should be avoided. <u>Recommendations for the use of antiarrhythmic drugs for pharmacologic cardioversion of POAF</u> • Restoration of sinus rhythm with pharmacologic cardioversion is reasonable in patients with symptomatic, hemodynamically stable POAF. Intravenous amiodarone can be useful for pharmacologic cardioversion of POAF. • It is reasonable to administer antiarrhythmic medications in an attempt to maintain sinus rhythm for patients with recurrent or refractory POAF. • Amiodarone, sotalol, flecainide, propafenone, or dofetilide can be useful to maintain sinus rhythm in patients with POAF, depending on underlying heart disease, renal status and other comorbidities. • Flecainide or propafenone may be considered for pharmacologic cardioversion of POAF and maintenance of sinus rhythm if the patient has had no prior history of myocardial infarction, coronary artery disease, impaired LV function, significant LV hypertrophy, or valvular heart disease that is considered moderate or greater. These agents may need to be combined with an AV nodal blocking agent. • Intravenous ibutilide or procainamide may be considered for pharmacologic conversion of POAF for patients with structural heart disease and new onset POAF, but no hypotension or manifestations of congestive heart failure. Serum electrolytes

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	and QTc interval must be within a normal range and patients must be closely monitored during and for at least six hours after the infusion if either ibutilide or procainamide. • Intravenous ibutilide or procainamide may be considered for patients with POAF and an accessory pathway. • Flecainide and propafenone should not be used to treat POAF in patients with a history of a prior myocardial infarction, coronary artery disease, and/or severe structural heart disease, including severe left ventricular hypertrophy, or significantly reduced left ventricular ejection fraction. • Dronedarone should not be used for treatment of POAF in patients with heart failure. <u>Recommendations for prevention of thromboembolism for patients with stable atrial fibrillation/flutter undergoing direct current cardioversion</u> • For stable patients with POAF of 48-hours duration or longer, anticoagulation (with warfarin for INR 2.0 to 3.0, a novel oral anti-coagulant [NOAC] or LMWH) is recommended for at least three weeks prior to and four weeks after cardioversion, regardless of the method (electrical or pharmacological) used to restore sinus rhythm. • During the first 48 hours after the onset of POAF, the need for anticoagulation before and after direct current (DC) cardioversion may be based on the patient's risk of thromboembolism (CHA2DS2-VASc score) balanced by the risk of postoperative bleeding. • For POAF lasting longer than 48 hours, as an alternative to three weeks of therapeutic anticoagulation prior to cardioversion of POAF, it is reasonable to perform TEE in search of thrombus in the LA or LA appendage, preferably with full anticoagulation at the time of TEE in anticipation of DC cardioversion after the TEE. • For POAF lasting longer than 48 hours in patients who are not candidates for TEE (e.g., post-esophageal surgery), an initial rate control strategy combined with therapeutic anticoagulation using warfarin (aiming for INR 2.0 to 3.0), a direct thrombin inhibitor (e.g. dabigatran), factor Xa inhibitor (e.g. rivaroxaban, apixaban), or LMWH is recommended for at least three weeks prior to and four weeks after cardioversion. • Anticoagulation recommendations for cardioversion of atrial flutter are similar to those for atrial fibrillation. • For patients with an identified thrombus, cardioversion should not be performed until a longer period of anticoagulation is achieved (usually at least three weeks) and in accordance with established AF guidelines. <u>Management of anticoagulation for new onset POAF</u> • For the prevention of strokes for patients who develop POAF lasting longer than 48 hours, it is recommended to administer antithrombotic medications similarly to non-surgical patients. Anticoagulation within the first 48-hours of POAF should be considered based on the CHA2DS2-VASc risk score of the patient for stroke weighed against the risk of postoperative bleeding. • New oral anticoagulants (dabigatran, rivaroxaban, apixaban) are reasonable as an alternative to warfarin for patients who do not have a prosthetic heart valve, hemodynamically significant valve disease, and/or severe renal impairment or risk of GI bleeding. • It is reasonable to continue anticoagulation therapy for four weeks after the return of sinus rhythm because of the possibility of slowly resolving impairment of atrial contraction with an associated ongoing risk for thrombus formation and for delayed embolic events. • New oral anticoagulants should be avoided for patients at risk for serious bleeding

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	(including GI bleeding) as they cannot be readily reversed. However, their use may be recommended in situations where achievement of a therapeutic INR with warfarin has proved to be difficult.
Eighth Joint National Committee (JNC 8): **2014 Evidence-based Guideline for the Management of High Blood Pressure in Adults (2014)**[26]	• Pharmacologic treatment should be initiated in patients ≥60 years of age to lower blood pressure at systolic blood pressure ≥150 mm Hg or diastolic blood pressure ≥90 mm Hg and to a goal systolic blood pressure <150 mm Hg and goal diastolic blood pressure <90 mm Hg. Adjustment of treatment is not necessary if treatment results in lower blood pressure and treatment is well tolerated and without adverse effects on health or quality of life. • In patients <60 years of age, pharmacologic treatment should be initiated to lower blood pressure at diastolic blood pressure ≥90 mm Hg to a goal diastolic blood pressure <90 mm Hg. • In patients <60 years of age, pharmacologic treatment should be initiated to lower blood pressure at systolic blood pressure ≥150 mm Hg to a goal diastolic blood pressure <140 mm Hg. • For patients ≥18 years of age with chronic kidney disease or diabetes, pharmacologic treatment should be initiated to lower blood pressure at systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg and to a goal systolic blood pressure <140 mm Hg and goal diastolic blood pressure <90 mm Hg. • Initial antihypertensive treatment for the general nonblack population, including those with diabetes, should include thiazide-type diuretic, calcium channel blocker (CCB), ACE inhibitor, or ARB. • Initial antihypertensive treatment for the general black population, including those with diabetes, should include thiazide-type diuretic or CCB. • For patients ≥18 years of age with chronic kidney disease regardless of race or diabetes status, initial (or add-on) treatment should include an ACE inhibitor or ARB to improve kidney outcomes. • The main goal of antihypertensive treatment is to attain and maintain goal blood pressure. • If goal blood pressure is not attained within a month of treatment, the dose of the initial drug should be increased or second drug from the thiazide-type diuretic, CCB, ACE inhibitor, or ARB classes should be added. • If goal is not achieved with two drugs, a third drug from the thiazide-type diuretic, CCB, ACE inhibitor, or ARB classes should be added. • An ACE inhibitor and ARB should not be used together. • Antihypertensive classes can be used if the patient is unable to achieve goal blood pressure with three agents or had a contraindication to a preferred class. • If blood pressure is not able to be achieved or in complicated patients, referral to a hypertension specialist may be indicated.
International Society of Hypertension: **Global Hypertension Practice Guidelines (2020)**[27]	<u>Lifestyle modifications</u> • Lifestyle modification is the first line of antihypertensive treatment. • Salt reduction: Reduce salt added when preparing foods, and at the table. Avoid or limit consumption of high salt foods such as soy sauce, fast foods and processed food including breads and cereals high in salt. • Healthy diet: Eating a diet that is rich in whole grains, fruits, vegetables, polyunsaturated fats and dairy products and reducing food high in sugar, saturated fat and trans fats, such as the DASH diet. • Healthy drinks: Moderate consumption of coffee, green and black tea. Other beverages that can be beneficial include karkadé (hibiscus) tea, pomegranate juice, beetroot juice and cocoa. • Moderation of alcohol consumption: The recommended daily limit for alcohol consumptions is 2 standard drinks for men and 1.5 for women (10 g alcohol/standard drink). Avoid binge drinking. • Weight reduction: Body weight control is indicated to avoid obesity. Particularly

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	abdominal obesity should be managed. Ethnic-specific cut-offs for BMI and waist circumference should be used. Alternatively, a waist-to-height ratio <0.5 is recommended for all populations. • Smoking cessation: Smoking is a major risk factor for cardiovascular disease (CVD), COPD and cancer. Smoking cessation and referral to smoking cessation programs are advised. • Regular physical activity: Studies suggest that regular aerobic and resistance exercise may be beneficial for both the prevention and treatment of hypertension. Moderate intensity aerobic exercise (walking, jogging, cycling, yoga, or swimming) for 30 minutes on five to seven days per week Strength training also can help reduce blood pressure. Performance of resistance/strength exercises on two to three days per week. • Reduce stress and induce mindfulness: Stress should be reduced and mindfulness or meditation introduced into the daily routine. • Reduce exposure to air pollution and cold temperature: Evidence from studies support a negative effect of air pollution on blood pressure in the long-term. <u>Pharmacological Treatment</u> • Ideal characteristics of drug treatment o Treatments should be evidence-based in relation to morbidity/mortality prevention. o Use a once-daily regimen which provides 24-hour blood pressure control. o Treatment should be affordable and/or cost-effective relative to other agents. o Treatments should be well-tolerated. o Evidence of benefits of use of the medication in populations to which it is to be applied. • General scheme for drug treatment o Lifestyle modification is the first line of antihypertensive treatment. o Grade 1 hypertension (BP 140 to 159/ 90 to 99): Immediate drug treatment in high-risk patients or those with CVD, chronic kidney disease (CKD), diabetes mellitus (DM), or hypertension-mediated organ damage (HMOD). Drug treatment after three to six months of lifestyle intervention if BP still not controlled in low to moderate risk patients. o Grade 2 hypertension (BP ≥160/100): Immediate drug treatment in all patients. • Core drug-treatment strategy o Step 1: Dual low-dose combination (ACE inhibitor or ARB plus dihydropyridine-calcium channel blockers (DHP-CCB)); consider monotherapy in low-risk grade 1 hypertension or in very old (≥80 years) or frail patients; consider ACE/ARB plus thiazide-like diuretic in post-stroke, very elderly, incipient HF, or CCB intolerance; consider ACE/ARB plus DHP-CCB or DHP-CCB plus thiazide-like diuretics in black patients. o Step 2: Dual full-dose combination (ACE inhibitor or ARB plus DHP-CCB); consider monotherapy in low-risk grade 1 hypertension or in very old (≥80 years) or frail patients; consider ACE/ARB plus thiazide-like diuretic in post-stroke, very elderly, incipient HF, or CCB intolerance. o Step 3: Triple combination (ACE/ARB plus DHP-CCB plus thiazide-like diuretic). o Step 4, resistant hypertension: triple combination plus spironolactone or other drug, alternatives include amiloride, doxazosin, eplerenone, clonidine, or β-blocker. Caution with spironolactone or other potassium sparing diuretics when estimated GFR <45 mL/min/1.73m^2 or K+ >4.5 mmol/L. o Consider β-blockers at any treatment step when there is a specific

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	indication for their use, e.g., heart failure, angina, post-MI, atrial fibrillation, or younger women planning pregnancy or pregnant.

Hypertension Canada: **2020 Guidelines for the Prevention, Diagnosis, Risk Assessment, and Treatment of Hypertension in Adults and Children (2020)**[28]	Indications for drug therapy for adults with hypertension without compelling indications for specific agents
	• Antihypertensive therapy should be prescribed for average diastolic blood pressure (DBP) measurements of ≥100 mmHg or average systolic blood pressure (SBP) measurements of ≥160 mmHg in patients without macrovascular target organ damage or other cardiovascular risk factors.
	• Antihypertensive therapy should be strongly considered for average DPB readings ≥90 mmHg or for average SBP readings ≥140 mmHg in the presence of macrovascular target organ damage or other independent cardiovascular risk factors.
	• For high-risk patients, aged 50 years or older, with SBP levels ≥130 mmHg, intensive management to target a SBP <120 mmHg should be considered. Patient selection for intensive management is recommended and caution should be taken in certain high-risk groups.
	
	Indications for drug therapy for adults with diastolic and with or without systolic hypertension
	• Initial therapy should be with either monotherapy or single pill combination (SPC).
	  ○ Recommended monotherapy choices are:
	  ▪ A thiazide/thiazide-like diuretic, with longer-acting diuretics preferred;
	  ▪ A β-blocker (in patients <60 years of age);
	  ▪ An angiotensin-converting enzyme (ACE) inhibitor (in nonblack patients);
	  ▪ An angiotensin receptor blocker (ARB); or
	  ▪ A long-acting calcium channel blocker (CCB).
	  ○ Recommended SPC choices are those in which an ACE inhibitor is combined with a CCB, ARB with a CCB, or ACE inhibitor or ARB with a diuretic.
	  ○ Hypokalemia should be avoided in patients treated with thiazide/thiazide-like diuretic monotherapy.
	• Additional antihypertensive drugs should be used if target BP levels are not achieved with standard-dose monotherapy. Add-on drugs should be chosen from first-line choices. Useful choices include a thiazide/thiazide-like diuretic or CCB with either: ACE inhibitor, ARB, or β-blocker. Caution should be exercised in combining a nondihydropyridine CCB and a β-blocker. The combination of an ACE inhibitor and an ARB is not recommended.
	• If BP is still not controlled with a combination of two or more first-line agents, or there are adverse effects, other antihypertensive drugs may be added.
	• Possible reasons for poor response to therapy should be considered.
	• α-Blockers are not recommended as first-line agents for uncomplicated hypertension; β-blockers are not recommended as first-line therapy for uncomplicated hypertension in patients ≥60 years of age; and ACE inhibitors are not recommended as first-line therapy for uncomplicated hypertension in black patients. However, these agents may be used in patients with certain comorbid conditions or in combination therapy.
	
	Indications for drug therapy for adults with isolated systolic hypertension
	• Initial therapy should be single-agent therapy with a thiazide/thiazide-like diuretic, a long-acting dihydropyridine CCB, or an ARB. If there are adverse effects, another drug from this group should be substituted. Hypokalemia should be avoided in patients treated with thiazide/thiazide-like diuretic monotherapy.
	• Additional antihypertensive drugs should be used if target BP levels are not achieved with standard-dose monotherapy. Add-on drugs should be chosen from first-line options.

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	• If BP is still not controlled with a combination of two or more first-line agents, or there are adverse effects, other classes of drugs (such as α-blockers, ACE inhibitors, centrally acting agents, or nondihydropyridine CCBs) may be combined or substituted. • Possible reasons for poor response to therapy should be considered. • α-Blockers are not recommended as first-line agents for uncomplicated isolated systolic hypertension; and β-blockers are not recommended as first-line therapy for isolated systolic hypertension in patients ≥60 years of age. However, both agents may be used in patients with certain comorbid conditions or in combination therapy. <u>Guidelines for hypertensive patients with coronary artery disease (CAD)</u> • For most hypertensive patients with CAD, an ACE inhibitor or ARB is recommended. • For hypertensive patients with CAD, but without coexisting systolic heart failure, the combination of an ACE inhibitor and ARB is not recommended. • For high-risk hypertensive patients, when combination therapy is being used, choices should be individualized. The combination of an ACE inhibitor and a dihydropyridine CCB is preferable to an ACE inhibitor and a thiazide/thiazide-like diuretic in selected patients. • For patients with stable angina pectoris but without previous heart failure, myocardial infarction, or coronary artery bypass surgery, either a β-blocker or CCB can be used as initial therapy. • Short-acting nifedipine should not be used. • When decreasing SBP to target levels in patients with established CAD (especially if isolated systolic hypertension is present), be cautious when the DBP is ≤60 mmHg because of concerns that myocardial ischemia might be exacerbated, especially in patients with left ventricular hypertrophy (LVH). <u>Guidelines for patients with hypertension who have had a recent myocardial infarction</u> • Initial therapy should include a β-blocker as well as an ACE inhibitor. • An ARB can be used if the patient is intolerant of an ACE inhibitor. • CCBs may be used in patients after myocardial infarction when β-blockers are contraindicated or not effective. Nondihydropyridine CCBs should not be used when there is heart failure, evidenced by pulmonary congestion on examination or radiography. <u>Treatment of hypertension in association with heart failure</u> • In patients with systolic dysfunction (ejection fraction <40%), ACE inhibitors and β-blockers are recommended for initial therapy. Aldosterone antagonists (mineralocorticoid receptor antagonists) may be combined in treatment for patients with a recent cardiovascular hospitalization, acute myocardial infarction, elevated B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide level, or New York Heart Association (NYHA) Class II-IV symptoms. Careful monitoring for hyperkalemia is recommended when combining an aldosterone antagonist with ACE inhibitor or ARB treatment. Other diuretics are recommended as additional therapy if needed. Beyond considerations of BP control, doses of ACE inhibitors or ARBs should be titrated to those reported to be effective in trials unless adverse effects become manifest. • An ARB is recommended if ACE inhibitors are not tolerated. • A combination of hydralazine and isosorbide dinitrate is recommended if ACE inhibitors and ARBs are contraindicated or not tolerated. • For hypertensive patients whose BP is not controlled, an ARB may be combined with an ACE inhibitor and other antihypertensive drug treatment. Careful monitoring should be used if combining an ACE inhibitor and an ARB because of

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	potential adverse effects such as hypotension, hyperkalemia, and worsening renal function. Additional therapies may also include dihydropyridine CCBs. • An angiotensin receptor-neprilysin inhibitor (ARNI) should be used in place of an ACE inhibitor or ARB for patients with HfrEF (<40%) who remain symptomatic despite treatment with appropriate dose of guideline directed HF therapy. Eligible patients must have a serum potassium <5.2 mmol/L, an eGFR ≤30 mL/min/1.73m^2 and close surveillance of serum potassium and creatinine. <u>Treatment of hypertension in association with stroke</u> • BP management in acute ischemic stroke (onset to 72 hours) o Please refer to Stroke Best Practice recommendations. • BP management after acute ischemic stroke o Strong consideration should be given to the initiation of antihypertensive therapy after the acute phase of a stroke or transient ischemic attack. o After the acute phase of a stroke, BP-lowering treatment is recommended to a target of consistently <140/90 mmHg. o Treatment with an ACE inhibitor and thiazide/thiazide-like diuretic combination is preferred. o For patients with stroke, the combination of an ACE inhibitor and ARB is not recommended. • BP management in hemorrhagic stroke (onset to 72 hours) o Please refer to Stroke Best Practice recommendations. <u>Treatment of hypertension in association with LVH</u> • Hypertensive patients with LVH should be treated with antihypertensive therapy to decrease the rate of subsequent cardiovascular events. • The choice of initial therapy can be influenced by the presence of LVH. Initial therapy can be drug treatment using ACE inhibitors, ARBs, long-acting CCBs, or thiazide/thiazide-like diuretics. Direct arterial vasodilators such as hydralazine or minoxidil should not be used. <u>Treatment of hypertension in association with nondiabetic chronic kidney disease</u> • Individualize BP targets in patients with chronic kidney disease. Consider intensive targets (SBP <120 mmHg) in appropriate patients. • For patients with hypertension and proteinuric chronic kidney disease (urinary protein >150 mg per 24 hours or albumin to creatinine ratio >30 mg/mmol), initial therapy should be an ACE inhibitor or an ARB if there is intolerance to ACE inhibitors. • In most cases, combination therapy with other antihypertensive agents might be needed to reach target BP levels. • The combination of an ACE inhibitor and ARB is not recommended for patients with nonproteinuric chronic kidney disease. <u>Treatment of hypertension in association with renovascular disease</u> • Patients with hypertension attributable to atherosclerotic renal artery stenosis should be primarily medically managed because renal angioplasty and stenting offers no benefit over optimal medical therapy alone. • Renal artery angioplasty and stenting for atherosclerotic hemodynamically significant renal artery stenosis could be considered for patients with uncontrolled hypertension resistant to maximally tolerated pharmacotherapy, progressive renal function loss, and acute pulmonary edema. • Patients with confirmed renal fibromuscular dysplasia (FMD) should be referred to a hypertension specialist. • Renal artery angioplasty without stenting is recommended for treatment of FMD-related renal artery stenosis. Stenting is not recommended unless needed because of

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	a periprocedural dissection. Surgical revascularization should be considered in cases of complex lesions less amendable to angioplasty, stenosis associated with complex aneurysm, and restenosis despite two unsuccessful attempts of angioplasty. Treatment of hypertension in association with diabetes mellitus • Persons with diabetes mellitus should be treated to attain SBP of <130 mmHg and DBP of <80 mmHg. • For persons with cardiovascular or kidney disease, including microalbuminuria, or with cardiovascular risk factors in addition to diabetes and hypertension, an ACE inhibitor or an ARB is recommended as initial therapy. • For persons with diabetes and hypertension not included in other guidelines in this section, appropriate choices include (in alphabetical order): ACE inhibitors, ARBs, dihydropyridine CCBs, and thiazide/thiazide-like diuretics. • If target BP levels are not achieved with standard-dose monotherapy, additional antihypertensive therapy should be used. For persons in whom combination therapy with an ACE inhibitor is being considered, a dihydropyridine CCB is preferable to a thiazide/thiazide-like diuretic. Resistant hypertension • Resistant hypertension is defined as BP above target despite three or more BP-lowering drugs at optimal doses preferably including a diuretic (and usually a renin-angiotensin-aldosterone system blocker and a CCB. • Accurate office and out-of-office BP measurement is essential. • Other reasons for apparent resistant hypertension should be eliminated before diagnosing true resistant hypertension, including nonadherence, white coat effect, and secondary hypertension. • Pharmacotherapy with the additional use of spironolactone, bisoprolol, doxazosin, amiloride, eplerenone, or clonidine with the baseline regimen decreases BP significantly, with the greatest BP-lowering shown with spironolactone. • Patients with resistant hypertension should be referred to providers with expertise in diagnosis and management of hypertension. Hypertension and pediatrics • BP should be measured regularly in children three years of age or older; the auscultatory method is the gold-standard at present. • Initial therapy should be monotherapy, with an ACE inhibitor or ARB (not first-line in black children), or a long-acting dihydropyridine CCB. • The treatment t goal is systolic and diastolic office BP and/or ABPM < 95^{th} percentile or <90^{th} percentile in children with risk factors or target organ damage. • Complex cases should be referred to an expert in pediatric hypertension. Hypertension and pregnancy • Up to 7% of pregnancies are complicated by a hypertensive disorder of pregnancy, and approximately 5% of women will have chronic hypertension when they become pregnant. • The prevalence of hypertension in pregnancy is expected to increase with women becoming pregnant later in their reproductive years and the increasing prevalence of cardiovascular comorbidities such as increased preconception body mass index and maternal diabetes. • The possibility of pregnancy should be considered when managing women with hypertension who are of reproductive age. • Preconception counselling should be offered to all women with hypertension who are considering pregnancy. • ACE inhibitor and ARB therapy should be avoided before conception and during

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	pregnancy unless there is a compelling indication for their use (i.e., proteinuric kidney disease). • Hypertension during pregnancy can increase the risk of adverse maternal and fetal outcomes, including an increased risk of preeclampsia, placental abruption, prematurity, small for gestational age infants, stillbirth, and maternal renal and retinal injury, thus generally requires involvement of an interdisciplinary team including obstetrical care providers. • Antihypertensive therapy is recommended for average SBP measurements of ≥140 mmHg or DBP measurements of ≥90 mmHg in pregnant women with chronic hypertension, gestational hypertension, or preeclampsia. Initial antihypertensive therapy should be monotherapy from the following first-line drugs: oral labetalol, oral methyldopa, long-acting oral nifedipine, or other oral b-blockers (acebutolol, metoprolol, pindolol, and propranolol). Other antihypertensive drugs can be considered as second-line drugs including: clonidine, hydralazine, and thiazide diuretics. • Women with severe hypertension with SBP ≥160 mmHg or DBP ≥110 mmHg in pregnancy or postpartum require urgent antihypertensive therapy because it is considered an obstetrical emergency. • Antihypertensive drugs used in breastfeeding women include: labetalol, methyldopa, long-acting nifedipine, enalapril, or captopril.
European Society of Hypertension: **2023 Guidelines for the management of arterial hypertension (2023)**[29]	General recommendations for antihypertensive drug treatment • BP lowering should be prioritized over the selection of specific antihypertensive drug classes because treatment benefit largely originates from BP reduction. • Five major drug classes including, ACE inhibitors, ARBs, β-blockers, CCBs, and Thiazide/Thiazide-like diuretics have effectively reduced blood pressure and cardiovascular events in randomized controlled trials. These drugs and their combinations are recommended as the basis of antihypertensive treatment strategies. • Initiation of therapy with a two-drug combination is recommended for most hypertensive patients. Preferred combinations should comprise a RAS blocker (either an ACE inhibitor or an ARB) with a CCB or thiazide/thiazide-like diuretic. Other combinations of the five major drug classes can be used. • Initiation with monotherapy can be considered in patients with: grade 1 hypertension and low-risk if BP is only marginally elevated (less than 150 mmHg SBP and 95 mmHg DBP) high-normal BP and very high cardiovascular risk, frailty and/or and advance age. • If BP is not controlled with the initial two-drug combination by using the maximum recommended and tolerated dose of the respective components, treatment should be increased to a three-drug combination, usually a RAS blocker plus CCB plus thiazide/thiazide-like diuretic. • If BP is not controlled with a three-drug combination by using the maximum recommended and tolerated dose of the respective components, it is recommended to extend treatment according to the recommendations for resistant hypertension. • The use of single pill combinations should be preferred at any treatment step (i.e. during initiation of therapy with a two-drug combination and at any other step of treatment). • β-blocker should be used at initiation of therapy or at any treatment step as guideline-directed medical therapy (e.g., heart failure with reduced ejection fraction, anti-ischemic therapy in chronic coronary syndromes, heart rate control in atrial fibrillation). • β-blockers can be considered in the presence of several other conditions in which their use can be favorable. • The combination of two RAS blockers is not recommended due to increased risk of adverse events, in particular AKI.

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	True-resistant hypertension • In resistant hypertension, it is recommended to reinforce lifestyle measures. • Drugs that can be considered as additional therapy in patients with resistant hypertension are preferably spironolactone (or other MRA), or β-blocker or Alpha-1 blockers or centrally acting agents (clonidine), or amiloride. • Thiazide/thiazide-like diuretics are recommended in resistant hypertension if estimated eGFR is ≥30 mL/min/1.73m^2. • Loop diuretics may be considered in patients with an estimated eGFR < 45 mL/min/1.73m^2 and should be used if eGFR falls below 30 mL/min/1.73m^2. • Chlorthalidone (12.5 to 25 mg once daily) could be used with or without a loop diuretic if eGFR is <30 mL/min/1.73m^2. • Renal deprivation can be considered as an additional treatment option in patients with resistant hypertension if eGFR is >40 mL/min/1.73m^2. • Patients with resistant hypertension should be followed very closely. Follow-up includes periodical ambulatory blood pressure monitoring and assessment of hypertension-mediated organ damage, particularly kidney function and serum potassium levels. Regular use of home blood pressure monitoring and monitoring of drug adherence are desirable.
National Institute for Health and Clinical Excellence: **Hypertension in adults: diagnosis and management (2019)**[30]	Choosing antihypertensive drug treatment (for people with or without type II diabetes) • Where possible, recommend treatment with drugs taken only once a day. • Prescribe non-proprietary drugs where these are appropriate and minimize cost. • Offer people with isolated systolic hypertension (systolic blood pressure ≥160 mmHg) the same treatment as people with both raised systolic and diastolic blood pressure. • Offer antihypertensive drug treatment to women of child-bearing potential with diagnosed hypertension in line with recommendations in this guideline. For women considering pregnancy or who are pregnant or breastfeeding, manage hypertension in line with the recommendations on Management of pregnancy with chronic hypertension and Breastfeeding in 'Hypertension in pregnancy'. • When choosing antihypertensive drug treatment for adults of black African or African-Caribbean family origin, consider an angiotensin II receptor blocker, in preference to an angiotensin-converting enzyme inhibitor. Step one treatment • Patients <55 years of age should be offered a step one antihypertensive with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). • Offer an ACE inhibitor or an ARB to adults starting step 1 antihypertensive treatment who have type II diabetes and are of any age or family origin or those aged <55 years but not of black African or African-Caribbean family origin. • If an ACE inhibitor is not tolerated, offer an ARB. • Do not combine an ACE inhibitor with an ARB for the treatment of hypertension. • Offer a calcium channel blocker (CCB) to adults starting step 1 antihypertensive treatment who are >55 years of age and do not have diabetes and are of black African or African-Caribbean family origin and do not have type II diabetes and of any age. • If a CCB is not suitable, for example because of edema or intolerance, or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic. • If diuretic treatment is to be initiated or changed, offer a thiazide-like diuretic, such as indapamide in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide. • For adults with hypertension who are already receiving treatment with bendroflumethiazide or hydrochlorothiazide, who have stable, well-controlled blood pressure, continue with their treatment.

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	Step two treatment • Before considering next step treatment for hypertension discuss with the person if they are taking their medicine as prescribed and support adherence in line with NICE's guideline on "Medicines adherence: involving patients decisions about prescribed medicines and supporting adherence". • If hypertension is not controlled with a step one treatment of an ACE inhibitor or ARB, offer choice of one of the following drugs in addition to the step one treatment: a CCB or a thiazide-like diuretic. • If hypertension is not controlled in adults taking step one treatment of a CCB, offer the choice of one of the following drugs in addition to the step one treatment: an ACE inhibitor or an ARB or a thiazide-like diuretic. • If hypertension is not controlled in adults of black African or African–Caribbean family origin who do not have type 2 diabetes taking step one treatment, consider an ARB, in preference to an ACE inhibitor, in addition to step one treatment. Step three treatment • Before considering step three treatment, review the person's medications to ensure they are being taken at the optimal doses and discuss adherence (see recommendation under step two). • If hypertension is not controlled in adults taking step two treatment, offer a combination of an ACE inhibitor or ARB and a CCB and a thiazide-like diuretic. Step four treatment • If hypertension is not controlled in adults taking the optimal tolerated doses of an ACE inhibitor or an ARB plus a CCB and a thiazide-like diuretic, regard them as having resistant hypertension. • Before considering further treatment for a person with resistant hypertension, confirm elevated clinic blood pressure measurements using ambulatory or home blood pressure recordings, assess for postural hypotension, and discuss adherence. • For people with confirmed resistant hypertension, consider adding a fourth antihypertensive drug as step four treatment or seeking specialist advice. • Consider further diuretic therapy with low-dose spironolactone for adults with resistant hypertension starting step four treatment who have a blood potassium level of 4.5 mmol/l or less. Use particular caution in people with a reduced estimated glomerular filtration rate because they have an increased risk of hyperkalemia. • When using further diuretic therapy for step four treatment of resistant hypertension, monitor blood sodium and potassium and renal function within one month of starting treatment and repeat as needed thereafter. • Consider an alpha-blocker or beta-blocker for adults with resistant hypertension starting step four treatment who have a blood potassium level of more than 4.5 mmol/l. • If blood pressure remains uncontrolled in people with resistant hypertension taking the optimal tolerated doses of four drugs, seek specialist advice.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in Blacks (2010)**[31]	• To attain and maintain blood pressure (BP) below target levels, multiple antihypertensive drugs will be required in most hypertensive blacks. • Use of two-drug combination therapy when SBP is >15 mm Hg and/or DBP is >10 mm Hg above goal levels is increasingly recommended as first-line therapy. • Two-drug regimens have generally contained a thiazide-type diuretic; however, the combination of a calcium channel blocker (CCB) with either an ACE inhibitor or an ARB has been shown equally efficacious in BP lowering but with demonstrated superiority (CCB+ACE) for hard clinical outcomes compared with the same ACE inhibitor plus a thiazide-type diuretic.

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	• In secondary prevention patients, the combination therapy should include a drug(s) with the appropriate compelling indications. • Certain classes of antihypertensive medications, specifically diuretics and CCBs, lower BP on average more than β-blockers and renin-angiotensin system (RAS) blockers in black patients when used as monotherapies. • In the absence of compelling indications, when BP is near goal levels, monotherapy with a diuretic or a CCB is preferred. • Lifestyle modifications should be initiated in all patients with hypertension, whether or not pharmacotherapy is planned. • ACE inhibitors or ARBs are recommended as alternative monotherapy options in the treatment of hypertension in blacks. The rationale for their lower tier monotherapy recommendation is because they have consistently achieved lesser average reductions in BP relative to that observed with monotherapy using either a diuretic or CCB.
Kidney Disease Improving Clinical Outcomes Group: **KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease (2021)**[32]	<u>Blood pressure measurement</u> • The Work Group recommends standardized office blood pressure (BP) measurement in preference to routine office BP measurements for the management of high BP in adults. • The Work Group suggests that out-of-office BP measurements with ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM) be used to complement standardized office BP readings for the management of high BP. <u>Lifestyle interventions for lowering BP in patients with chronic kidney disease (CKD) not receiving dialysis</u> • The Work Group suggests targeting a sodium intake <2 grams of sodium per day (or <90 mmol of sodium per day, or <5 grams of sodium chloride per day) in patients with high BP and CKD. • The Work Group suggests that patients with high BP and CKD be advised to undertake moderate-intensity physical activity for a cumulative duration of at least 150 minutes per week, or to a level compatible with their cardiovascular and physical tolerance. <u>BP management in patients with CKD, with or without diabetes, not receiving dialysis</u> • The Work Group suggests that adults with high BP and CKD be treated with a target systolic BP (SBP) of <120 mmHg, when tolerated, using standardized office BP measurement. • The Work Group recommends starting renin-angiotensin-system inhibitors (RASi) (angiotensin-converting enzyme inhibitor [ACEi] or angiotensin II receptor blocker [ARB]) for people with high BP, CKD, and severely increased albuminuria without diabetes. • The Work Group suggests starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately increased albuminuria without diabetes. • The Work Group recommends starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately-to-severely increased albuminuria with diabetes. • The Work Group recommends avoiding any combination of ACEi, ARB, and direct renin inhibitor (DRI) therapy in patients with CKD, with or without diabetes. <u>BP management in kidney transplant recipients</u> • Treat adult kidney transplant recipients with high BP to a target BP of <130 mmHg systolic and <80 mmHg diastolic using standardized office BP measurement. • The Work Group recommends that a dihydropyridine calcium channel blocker (CCB) or an ARB be used as the first-line antihypertensive agent in adult kidney transplant recipients. <u>BP management in children with CKD</u>

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	• The Work Group suggests that in children with CKD, 24-hour mean arterial pressure by ABPM should be lowered to <50th percentile for age, sex, and height.
American College of Cardiology/ American Heart Association Task Force: **Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults (2017)**[33]	Initiation of Blood Pressure (BP) Treatment for Overall Cardiovascular Disease (CVD) Risk • Use of BP-lowering medications is recommended for secondary prevention of recurrent CVD events in patients with clinical CVD and an average systolic blood pressure (SBP) ≥130 mmHg or an average diastolic blood pressure (DBP) of ≥80 mmHg and for primary prevention in adults with an estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk of ≥10% and an average SBP of ≥130 mmHg or an average ≥80 mmHg. • Use of BP-lowering medication is recommended for primary prevention of CVD in adults with no history of CVD and with an estimated 10-year ASCVD risk <10% and an SBP of ≥140 mmHg or a DBP of ≥90 mmHg. • Simultaneous use of an angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), and/or renin inhibitor is potentially harmful and is not recommended to treat adults with hypertension. • For adults with confirmed hypertension and known CVD or 10-year ASCVD risk of ≥10%, a BP target <130/80 mmHg is recommended. For adults with confirmed hypertension without additional markers of increased CVD risk, a BP target <130/80 mmHg may be reasonable. • For initiation of antihypertensive drug therapy, first-line agents include thiazide diuretics, calcium channel blockers (CCBs), and ACE inhibitors or ARBs. • Initiation of antihypertensive drug therapy with two first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended in adults with stage 2 hypertension and an average BP >20/10 mmHg above their BP target. • Initiation of antihypertensive drug therapy with a single antihypertensive drug is reasonable in adults with stage 1 hypertension and BP goal <130/80 mmHg with dosage titration and sequential addition of other agents to achieve the BP target. Stable Ischemic Heart Disease (SIHD) • In adults with SIHD and hypertension, a BP target <130/80 is recommended. • Adults with SIHD and hypertension (BP ≥130/80 mmHg) should be treated with medications [e.g., guideline-directed medical therapy (GDMT) beta-blockers, ACE inhibitors, or ARBs] for compelling indications [e.g., previous myocardial infarction (MI), stable angina] as first-line therapy, with the addition of other drugs (e.g., dihydropyridine CCBs, thiazide diuretics, and/or mineralocorticoid receptor antagonists) as needed to further control hypertension. • In adults with SIHD with angina and persistent uncontrolled hypertension, the addition of dihydropyridine CCBs to GDMT beta-blockers is recommended. • In adults who have had a MI or acute coronary syndrome, it is reasonable to continue GDMT beta-blockers beyond three years as long-term therapy for hypertension. • Beta-blockers and/or CCBs might be considered to control hypertension in patients with coronary artery disease (CAD) had an MI more than three years ago and have angina. Heart Failure • In adults with increased risk of HF, the optimal BP in those with hypertension should be <130 mmHg. • Adults with HfrEF and hypertension should be prescribed GDMT titrated to attain a BP <130/80 mmHg. • Non-dihydropyridine CCBs are not recommended in the treatment of hypertension in adults with HfrEF. • In adults with HfpEF who present with symptoms of volume overload, diuretics

Clinical Guideline	Recommendations
	should be prescribed to control hypertension. • Adults with HfpEF and persistent hypertension after management of volume overload should be prescribed ACE inhibitors or ARBs and beta-blockers titrated to attain SBP <130 mmHg. CKD • Adults with hypertension and CKD should be treated to a BP goal <130/80 mmHg. • In adults with hypertension and CKD [stage 3 or higher or stage 1 or 2 with albuminuria (≥300 mg/d, or ≥300 mg/g albumin-to-creatinine ratio or the equivalent in the first morning void)], treatment with an ACE inhibitor is reasonable to slow kidney disease progression. Treatment with an ARB may be reasonable if an ACE inhibitor is not tolerated. • After kidney transplantation, it is reasonable to treat patients with hypertension to a BP goal <130/80 mmHg and with a CCB on the basis of improved glomerular filtration rate (GFR) and kidney survival. Cerebrovascular Disease • In adults with intracerebral hemorrhage (ICH) who present with SBP >220 mmHg, it is reasonable to use continuous intravenous (IV) drug infusion and close BP monitoring to lower levels. Immediate lowering of SBP to <140 mmHg in adults with spontaneous ICH who present within six hours of the acute event and have an SBP between 150 mmHg and 220 mmHg is not of benefit to reduce death or severe disability and can be potentially harmful. • Adults with acute ischemic stroke and elevated BP who are eligible for treatment with IV tissue plasminogen activator (tPA) should have their BP slowly lowered to <185/110 mmHg before thrombolytic therapy is initiated. • In adults with an acute ischemic stroke, BP should be <185/110 mmHg before administration of IV tPA and should be maintained below 180/105 mmHg for at least the first 24 hours after initiation drug therapy. • Starting or restarting antihypertensive therapy during hospitalization in patients with BP >140/90 mmHg who are neurologically stable is safe and reasonable to improve long-term BP control, unless contraindicated. • In patient with BP ≥220/120 mmHg who did not receive IV alteplase or endovascular treatment and have no comorbid conditions requiring acute antihypertensive treatment, the benefit of initiating or reinitiating treatment of hypertension within the first 48 to 72 hours is uncertain. It might be reasonable to lower BP by 15% during the first 24 hours after onset of stroke. In patients with BP <220/120 mmHg with the same conditions, initiating or reinitiating treatment of hypertension within the first 48 to 72 hours after an acute ischemic stroke is not effective to prevent death or dependency. • Adults with previously treated stroke or transient ischemic attack should be restarted on antihypertensive treatment after the first few days of the index event to reduce the risk of recurrent stroke and other vascular events. Treatment with a thiazide diuretic, ACE inhibitor, or ARB, or combination treatment consisting of a thiazide diuretic plus ACE inhibitor, is useful. • Adults not previously treated for hypertension who experienced a stroke or transient ischemic attack and have an established BP ≥140/90 mmHg should be prescribed antihypertensive treatment a few days after the index event to reduce the risk of recurrent stroke and other vascular event. • For adults who experience a stroke or transient ischemic attack, selection of specific drugs should be individualized on the basis of patient comorbidities and agent pharmacological class. • For adults who experience a stroke or transient ischemic attack, a BP goal <130/80 mmHg may be reasonable. • For adults with a lacunar stroke, a target SBP goal <130 mmHg may be reasonable.

Clinical Guideline	Recommendations
	• In adults previously untreated for hypertension who experience an ischemic stroke or transient ischemic attack and have an SBP <140 mmHg and a DBP <90 mmHg, the usefulness of initiating antihypertensive treatment is not well established. Peripheral Artery Disease (PAD) • Adults with hypertension and PAD should be treated similarly to patients with hypertension without PAD. Diabetes Mellitus (DM) • In adults with DM and hypertension, antihypertensive drug treatment should be initiated at a BP of ≥130/80 mmHg with a treatment goal <130/80 mmHg. • In adults with DM and hypertension, all first-line classes of antihypertensive agents (i.e., diuretics, ACE inhibitors, ARBs, and CCBs) are useful and effective. • In adults with DM and hypertension, ACE inhibitors or ARBs may be considered in the presence of albuminuria. Atrial Fibrillation, Valvular Heart Disease, and Aortic disease • Treatment of hypertension can be useful for prevention of recurrence of AF. • In adults with asymptomatic aortic stenosis, hypertension should be treated with pharmacotherapy, starting at a low dose and gradually titrating upward as needed. • In patients with chronic aortic insufficiency, treatment of systolic hypertension with agents that do not slow the heart rate (i.e., avoid beta-blockers) is reasonable. • Beta-blockers are recommended as the preferred antihypertensive agents in patients with hypertension and thoracic aortic disease. Racial and Ethnic Differences in Treatment • In black adults with hypertension but without HF or CKD, including those with DM, initial antihypertensive treatment should include a thiazide-type diuretic or CCB. Two or more antihypertensive medications are recommended to achieve a BP target <130/80 mmHg in most adults with hypertension, especially in black adults with hypertension. Pregnancy • Women with hypertension who become pregnant, or are planning to become pregnant, should be transitioned to methyldopa, nifedipine, and/or labetalol during pregnancy. • Women with hypertension who become pregnant should not be treated with ACE inhibitors, ARBs, or direct renin inhibitors. Older Persons • Treatment of hypertension with an SBP treatment goal <130 mmHg is recommended for noninstitutionalized ambulatory community-dwelling adults (≥65 years of age) with an average SBP of ≥130 mmHg. • For older adults (≥65 years of age) with hypertension and a higher burden of comorbidity and limited life expectancy, clinical judgment, patient preference, and a team-based approach to assess risk/benefit is reasonable for decisions regarding intensity of BP lowering and choice of antihypertensive drugs. Hypertensive Crises • In adults with a hypertensive emergency, admission to an intensive care unit is recommended for continuous monitoring of BP and target organ damage and for parenteral administration of an appropriate agent. • For adults with a compelling condition (i.e., aortic dissection, severe pre-eclampsia or eclampsia, or pheochromocytoma crisis), SBP should be reduced to <140 mmHg during the first hour and to <120 mmHg in aortic dissection.

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	• For adults without a compelling condition, SBP should be reduced by no more than 25% within the first hours; then, if stable, to 160/100 mmHg within the next two to six hours; and then cautiously to normal during the following 24 to 48 hours. Cognitive Decline and Dementia • In adults with hypertension, BP lowering is reasonable to prevent cognitive decline and dementia. Patients Undergoing Surgical Procedures • In patients with hypertension undergoing major surgery who have been on beta-blockers chronically, beta-blockers should be continued. • In patients with hypertension undergoing planned elective major surgery, it is reasonable to continue medical therapy for hypertension until surgery. • In patients with hypertension undergoing major surgery, discontinuation of ACE inhibitors or ARBs perioperatively may be considered. • In patients with planned elective major surgery and SBP ≥180 mmHg or DBP ≥110 mmHg, deferring surgery may be considered. • For patients undergoing surgery, abrupt pre-operative discontinuation of beta-blockers or clonidine is potentially harmful. • Beta-blockers should not be started on the day of surgery in beta-blocker-naïve patients. • Patients with intraoperative hypertension should be managed with IV medications until such time as oral medications can be resumed.
American Diabetes Association: **Standards of Medical Care in Diabetes (2023)**[34]	Hypertension/blood pressure control • Blood pressure should be measured at every routine visit. When possible, patients found to have elevated blood pressure (systolic blood pressure 120 to 129 mmHg and diastolic <80 mmHg) should have blood pressure confirmed using multiple readings, including measurements on a separate day, to diagnose hypertension. Patients with blood pressure ≥180/110 and cardiovascular disease could be diagnosed with hypertension at a single visit. • All hypertensive patients with diabetes should monitor their blood pressure at home. • For patients with diabetes and hypertension, blood pressure targets should be individualized through a shared decision-making process that addresses cardiovascular risk, potential adverse effects of antihypertensive medications, and patient preferences. • Individuals with diabetes and hypertension qualify for antihypertensive drug therapy when the blood pressure is persistently elevated ≥130/80 mmHg. The on-treatment target blood pressure goal is <130/80 mmHg, if it can be safely attained. • In pregnant patients with diabetes and preexisting hypertension, a blood pressure target of 110 to 135/85 is suggested in the interest of reducing the risk for accelerated maternal hypertension and minimizing impaired fetal growth. • For patients with blood pressure >120/80, lifestyle intervention consists of weight loss when indicated, a Dietary Approaches to Stop Hypertension (DASH)-style eating pattern including reducing sodium and increasing potassium intake, moderation of alcohol intake, and increased physical activity. • Patients with confirmed office-based blood pressure ≥130/80 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of pharmacologic therapy to achieve blood pressure goals. • Patients with confirmed office-based blood pressure ≥160/100 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of two drugs or a single pill combination of drugs demonstrated to reduce cardiovascular events in patients with diabetes. • Treatment for hypertension should include drug classes demonstrated to reduce cardiovascular events in patients with diabetes (ACE inhibitors, angiotensin

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	receptor blockers, thiazide-like diuretics, or dihydropyridine calcium channel blockers). ACE inhibitors or angiotensin receptor blockers are recommended first-line therapy for hypertension in people with diabetes and coronary artery disease. • Multiple-drug therapy is generally required to achieve blood pressure targets (but not a combination of ACE inhibitors and angiotensin receptor blockers). • An ACE inhibitor or angiotensin receptor blocker, at the maximum tolerated dose indicated for blood pressure treatment, is the recommended first-line treatment for hypertension in patients with diabetes and urinary albumin–to–creatinine ratio ≥300 mg/g creatinine or 30 to 299 mg/g creatinine. If one class is not tolerated, the other should be substituted. • For patients treated with an ACE inhibitor, angiotensin receptor blocker, or diuretic, serum creatinine/estimated glomerular filtration rate and serum potassium levels should be monitored at least annually. • Patients with hypertension who are not meeting blood pressure targets on three classes of antihypertensive medications (including a diuretic) should be considered for mineralocorticoid receptor antagonist therapy. Chronic kidney disease • At least once a year, assess urinary albumin (e.g., spot urinary albumin–to–creatinine ratio) and estimated glomerular filtration rate in patients with type 1 diabetes with duration of five or more years and in all patients with type 2 diabetes. • In people with established diabetic kidney disease, urinary albumin (e.g., spot urinary albumin-to-creatinine ratio) and estimated glomerular filtration rate should be monitored one to four times per year depending on the stage of the disease. Optimize glucose control to reduce the risk or slow the progression of chronic kidney disease (CKD). • For patients with type 2 diabetes and diabetic kidney disease, use of a sodium-glucose cotransporter 2 inhibitor in patients with an estimated glomerular filtration rate ≥20 mL/min/1.73 m^2 and urinary albumin ≥200 mg/g creatinine is recommended to reduce CKD progression and cardiovascular events. • For patients with type 2 diabetes and diabetic kidney disease, use of a sodium–glucose cotransporter 2 inhibitor is recommended to reduce chronic kidney disease progression and cardiovascular events in patients with an estimated glomerular filtration rate ≥20 mL/min/1.73 m^2 and urinary albumin ranging from normal to 200 mg/g creatinine. • In people with type 2 diabetes and diabetic kidney disease, consider use of sodium–glucose cotransporter 2 inhibitors (if estimated glomerular filtration rate is ≥20 mL/min/1.73 m^2), a glucagon-like peptide 1 agonist, or a nonsteroidal mineralocorticoid receptor antagonist (if estimated glomerular filtration rate is ≥25 mL/min/1.73 m^2) additionally for cardiovascular risk reduction. • In people with chronic kidney disease and albuminuria who are at increased risk for cardiovascular events or chronic kidney disease progression, a nonsteroidal mineralocorticoid receptor antagonist shown to be effective in clinical trials is recommended to reduce chronic kidney disease progression and cardiovascular events. • Optimize blood pressure control and reduce blood pressure variability to reduce the risk or slow the progression of CKD. • Do not discontinue renin-angiotensin system blockade for minor increases in serum creatinine (≤30%) in the absence of volume depletion. • For people with nondialysis-dependent stage 3 or higher CKD, dietary protein intake should be a maximum of 0.8 g/kg body weight per day (the recommended daily allowance). For patients on dialysis, higher levels of dietary protein intake should be considered, since protein energy wasting is a major problem in some dialysis patients. • In nonpregnant patients with diabetes and hypertension, either an ACE inhibitor or

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	an angiotensin receptor blocker is recommended for those with modestly elevated urinary albumin–to–creatinine ratio (30 to 299 mg/g creatinine) and is strongly recommended for those with urinary albumin–to–creatinine ratio ≥300 mg/g creatinine and/or estimated glomerular filtration rate <60 mL/min/1.73 m^2. • Periodically monitor serum creatinine and potassium levels for the development of increased creatinine and hyperkalemia when ACE inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists are used, or hypokalemia when diuretics are used. • An ACE inhibitor or an angiotensin receptor blocker is not recommended for the primary prevention of CKD in patients with diabetes who have normal blood pressure, normal urinary albumin–to–creatinine ratio (<30 mg/g creatinine), and normal estimated glomerular filtration rate. • Patients should be referred for evaluation by a nephrologist if they have continuously increasing urinary albumin levels and/or continuously decreasing estimated glomerular filtration rate and an estimated glomerular filtration rate <30 mL/min/1.73 m^2. • Promptly refer to a nephrologist for uncertainty about the etiology of kidney disease, difficult management issues, and rapidly progressing kidney disease.

*Agent not available in the United States.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the miscellaneous calcium-channel blocking agents are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Calcium-Channel Blocking Agents, Miscellaneous[1,2,5-12]

Indication	Diltiazem	Verapamil
Angina Pectoris		
Angina due to coronary artery spasm	✔ (tablet, ER capsule [Cardizem CD®])	
Chronic stable angina	✔	✔ (tablet)
Unstable angina		✔ (tablet)
Vasospastic angina		✔ (tablet)
Arrhythmias		
Control of ventricular rate at rest and during stress in patients with chronic atrial flutter and/or atrial fibrillation in association with digitalis		✔ (tablet)
Prophylaxis of repetitive paroxysmal supraventricular tachycardia		✔ (tablet)
Rapid conversion to sinus rhythm of paroxysmal supraventricular tachycardias	✔ (injection)	✔ (injection)
Temporary control of rapid ventricular rate in atrial flutter or atrial fibrillation	✔ (injection)	✔ (injection)
Hypertension		
Hypertension	✔ * (ER)	✔

*May be used alone or in combination with other antihypertensive agents.
ER=extended-release

IV. Pharmacokinetics

The pharmacokinetic parameters of the miscellaneous calcium-channel blocking agents are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Calcium-Channel Blocking Agents, Miscellaneous[2]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Diltiazem*	35 to 40	77 to 93	Liver, extensive (% not reported)	Renal (35) Feces (60 to 65)	3 to 10
Verapamil*	20 to 35	88 to 94	Liver (65 to 80)	Renal (70) Feces (9 to 16)	4 to 12

*Immediate-release

V. Drug Interactions

Major drug interactions with the miscellaneous calcium-channel blocking agents are listed in Table 5.

Table 5. Major Drug Interactions with the Calcium-Channel Blocking Agents, Miscellaneous[2]

Generic Name(s)	Interaction	Mechanism
Calcium-channel blocking agents, miscellaneous (diltiazem, verapamil)	Macrolides	Increased serum levels of macrolide antibiotics may result if administered with calcium-channel blocking agents, miscellaneous, due to the inhibitory effect on CYP3A4. Coadministration should be avoided.
Calcium-channel blocking agents, miscellaneous (diltiazem, verapamil)	Narcotic Analgesics	Calcium-channel blocking agents, miscellaneous may increase plasma concentrations of narcotic analgesics, increasing the potential for enhanced pharmacologic effects and toxicity. Inhibition of CYP3A4 isoenzyme by Calcium-channel blocking agents, miscellaneous may decrease the metabolic elimination of narcotic analgesics.
Calcium-channel blocking agents, miscellaneous (diltiazem, verapamil)	Vasopressin Receptor Antagonists	Plasma concentrations and pharmacologic effects of vasopressin receptor antagonists may be increased by diltiazem. Inhibition of CYP3A isoenzymes by diltiazem may decrease the metabolic elimination of vasopressin receptor antagonists.
Calcium-channel blocking agents, miscellaneous (diltiazem, verapamil)	Amiodarone	Concurrent use of amiodarone and calcium channel blockers may result in bradycardia, atrioventricular block and/or sinus arrest.
Calcium-channel blocking agents, miscellaneous (diltiazem, verapamil)	Colchicine	Plasma concentrations of colchicine may be increased. Colchicine toxicity may occur. Inhibition of CYP3A4 and/or efflux transporter P-glycoprotein diltiazem may increase the absorption and decrease the metabolic elimination of colchicine.
Calcium-channel blocking agents, miscellaneous (diltiazem, verapamil)	Carbamazepine	Increased serum levels of carbamazepine may result if administered with diltiazem, increasing the risk of greater effect and toxicity, due to inhibition of carbamazepine metabolism by diltiazem.
Calcium-channel blocking agents, miscellaneous (diltiazem, verapamil)	Cyclosporine	Increased serum levels of cyclosporine may result if administered with diltiazem, due to inhibition of cyclosporine metabolism by diltiazem.
Calcium-channel blocking agents, miscellaneous (diltiazem, verapamil)	Everolimus	Pharmacologic effects and plasma concentrations of everolimus may be increased by diltiazem. Inhibition of CYP3A4 and P-glycoprotein by diltiazem may decrease the metabolic elimination of everolimus.
Calcium-channel blocking agents, miscellaneous	Ibrutinib	Diltiazem inhibits CYP3A4 metabolism of ibrutinib, thereby increasing plasma concentrations, pharmacologic effects, and risk of toxicity (e.g., hemorrhage, renal toxicity).

Generic Name(s)	Interaction	Mechanism
(diltiazem, verapamil)		
Calcium-channel blocking agents, miscellaneous (diltiazem, verapamil)	Lomitapide	Diltiazem inhibits CYP3A4 metabolism of lomitapide, thereby increasing plasma concentrations, pharmacologic effects, and risk of adverse reactions, including hepatotoxicity.
Calcium-channel blocking agents, miscellaneous (diltiazem, verapamil)	Ranolazine	Increased serum levels of ranolazine may result if administered with diltiazem, due to diltiazem's inhibitory effect on CYP3A4. Coadministration should be avoided due to the increased risk of QTc prolongation, torsades de pointes arrhythmias and death.
Calcium-channel blocking agents, miscellaneous (diltiazem, verapamil)	HMG CoA reductase inhibitors	Plasma concentrations and pharmacologic effects of statins may be increased by co-administration. The risk of myopathy and rhabdomyolysis may be increased. Inhibition of CYP3A4 isoenzymes by miscellaneous calcium-channel blockers may decrease the metabolic elimination of statins.
Calcium-channel blocking agents, miscellaneous (diltiazem)	Benzodiazepines	Increased serum levels of benzodiazepines may result if administered with diltiazem, increasing the risk of central nervous system depression, due to decreased metabolism of benzodiazepines.
Calcium-channel blocking agents, miscellaneous (diltiazem)	β-Blockers	Increased serum levels of β-blockers may result if administered with diltiazem, increasing the risk of symptomatic bradycardia, due to decreased metabolism of β-blockers and additive pharmacologic effects.
Calcium-channel blocking agents, miscellaneous (diltiazem)	Cilostazol	Pharmacologic effects of cilostazol may be increased by diltiazem. Elevated plasma concentrations with toxicity may occur. Inhibition of CYP3A4 isoenzymes by diltiazem may decrease the metabolic elimination of cilostazol.
Calcium-channel blocking agents, miscellaneous (diltiazem)	Cisapride	Concurrent use may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
Calcium-channel blocking agents, miscellaneous (diltiazem)	Corticosteroids	Diltiazem may increase the pharmacologic effects of corticosteroids. Inhibition of CYP3A4 isoenzymes by diltiazem may decrease the metabolic elimination of corticosteroids.
Calcium-channel blocking agents, miscellaneous (diltiazem)	Digoxin	Increased serum levels of digoxin may result, increasing the risk of digoxin toxicity, if administered with diltiazem, due to decreased renal clearance of digoxin.
Calcium-channel blocking agents, miscellaneous (diltiazem)	HIV Protease Inhibitors	Plasma concentrations and pharmacologic effects of diltiazem may be increased by HIV protease inhibitors. An additive effect on the PR interval has also been demonstrated. Plasma concentrations and pharmacologic effects of diltiazem may be increased by HIV protease inhibitors.
Calcium-channel blocking agents, miscellaneous (diltiazem)	Macrolide immuno-suppressives	Plasma trough concentrations of macrolide immunosuppressives may be increased by diltiazem. Neurologic toxicity may occur. Diltiazem may increase the plasma trough concentrations of macrolide immunosuppressives. Neurologic toxicity may occur.
Calcium-channel blocking agents, miscellaneous (diltiazem)	Theophyllines	The pharmacologic and toxic effects of theophyllines may be increased due to the inhibition of metabolism of theophylline by diltiazem.
Calcium-channel	β-Blockers	Effects of β-blockers and diltiazem may be increased, close

Generic Name(s)	Interaction	Mechanism
blocking agents, miscellaneous (verapamil)		monitoring of cardiac function is recommended. Diltiazem may inhibit the metabolism of some β-blockers (atenolol, metoprolol and propranolol), leading to increased effects of these β-blockers.
Calcium-channel blocking agents, miscellaneous (verapamil)	Digoxin	Verapamil may alter the pharmacokinetics and increase serum concentrations of digoxin. Verapamil may decrease nonrenal and total digoxin clearance.
Calcium-channel blocking agents, miscellaneous (verapamil)	Dofetilide	Increase serum levels and effects of dofetilide may occur if coadministered with verapamil, increasing the risk of arrhythmia.
Calcium-channel blocking agents, miscellaneous (verapamil)	Quinidine	Pharmacologic effects of quinidine may be increased. This combination may produce marked hypotension. Verapamil inhibits the hepatic metabolism of quinidine.
Calcium-channel blocking agents, miscellaneous (verapamil)	Aldosterone Blockers	Verapamil may increase plasma concentrations and pharmacologic or toxic effects of aldosterone blockers. Inhibition of CYP3A4 isoenzymes by verapamil may decrease the metabolic elimination of aldosterone blockers.
Calcium-channel blocking agents, miscellaneous (verapamil)	Clonidine	Sinus bradycardia, atrioventricular block and severe hypotension may occur with coadministration of clonidine and verapamil.
Calcium-channel blocking agents, miscellaneous (verapamil)	Dronedarone	Plasma concentrations and pharmacologic effects of dronedarone may be increased by verapamil. Dronedarone may also increase the plasma concentrations and pharmacologic effects of verapamil. Additionally, verapamil may enhance the electrophysiologic effects of dronedarone.
Calcium-channel blocking agents, miscellaneous (verapamil)	Flecainide	Increased risk of cardiotoxic effects may occur when flecainide and verapamil are coadministered. Cardiogenic shock or asystole may develop. Pharmacologic effects may be additive or synergistic.
Calcium-channel blocking agents, miscellaneous (verapamil)	Nondepolarizing muscle relaxants	Increased serum levels of nondepolarizing muscle relaxants may result, increasing the risk of respiratory depression, if coadministered with verapamil, due to calcium's role on muscle contraction.
Calcium-channel blocking agents, miscellaneous (verapamil)	Quinazolines	The combination of verapamil and quinazolines may produce an acute hypotensive effect which is greater than when either drug is taken alone. Verapamil may decrease the first-pass hepatic metabolism and increase the bioavailability of quinazolines.
Calcium-channel blocking agents, miscellaneous (verapamil)	Rifampin	Decreased serum levels of verapamil may result if coadministered with rifampin, due to increased metabolism of verapamil.

CYP=cytochrome P450 isoenzymes, HIV=human immunodeficiency virus, HMG CoA=3-hydroxy-3-methyl-glutaryl-CoA

VI. Adverse Drug Events

The most common adverse drug events reported with the miscellaneous calcium-channel blocking agents are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Calcium-Channel Blocking Agents, Miscellaneous[1,2,5-12]

Adverse Events	Diltiazem	Verapamil
Cardiovascular		
Angina	-	<1
Arrhythmia	<2	-
Atrial fibrillation	-	✔
Atrioventricular dissociation	-	<1
Atrioventricular block	2 to 8	1 to 2
Bradycardia	2 to 6	1
Bundle branch block	<2	-
Chest pain	-	<1
Claudication	-	<1
Congestive heart failure	<2	2
Edema	2 to 15	-
Extrasystoles	2	-
Flushing	1 to 2	1
Hypotension	<4	3
Myocardial infarction	-	<1
Palpitations	1 to 2	<1
Peripheral edema	2 to 8	2 to 4
Postural hypotension	-	<1
Syncope	<2	<1
Tachycardia	<2	-
Vasodilation	2 to 3	-
Ventricular fibrillation	-	✔
Central Nervous System		
Cerebrovascular accident	-	<1
Confusion	-	<1
Depression	<2	-
Dizziness	3 to 10	1 to 5
Fatigue	-	2 to 5
Headache	5 to 12	1 to 12
Insomnia	-	<1
Lethargy	-	3
Nervousness	2	-
Paresthesia	-	1
Psychotic symptoms	-	<1
Sleep disturbance	-	1
Somnolence	-	<1
Tremor	<2	<1
Vertigo	-	<1
Dermatologic		
Alopecia	-	<1
Ecchymosis	-	<1
Erythema multiforme	-	<1
Hair color change	-	✔
Hyperhidrosis	-	<1
Hyperkeratosis	-	<1
Petechiae	<2	-
Photosensitivity	<2	-
Rash	1 to 4	1 to 2
Stevens-Johnson syndrome	<2	-
Toxic epidermal necrolysis	<2	-
Endocrine and Metabolic		

Adverse Events	Diltiazem	Verapamil
Gout	1 to 2	-
Gynecomastia	-	<1
Hyperprolactinemia/galactorrhea	-	<1
Gastrointestinal		
Abdominal discomfort	-	<1
Constipation	<4	7 to 12
Diarrhea	1 to 2	2
Dry mouth	-	<1
Dysgeusia	<2	-
Dyspepsia	1 to 6	3
Gingival hyperplasia	<2	<19
Nausea	-	1 to 3
Vomiting	2	-
Genitourinary		
Acute renal failure	-	✔
Albuminuria	-	-
Crystalluria	-	-
Impotence	-	<1
Nocturia	-	-
Polyuria	-	<1
Sexual dysfunction	-	-
Spotty menstruation	-	<1
Hematological		
Hemolytic anemia	<2	-
Purpura	-	<1
Thrombocytopenia	<2	-
Laboratory Test Abnormalities		
Alkaline phosphatase increase	<2	-
ALT increased	<2	-
AST increased	<2	-
Liver enzyme elevations	-	1
Musculoskeletal		
Arthralgia	-	<1
Extrapyramidal symptoms	<2	-
Muscle cramps	-	<1
Myalgia	2	1
Pain	6	2
Paresthesia	-	1
Weakness	1 to 4	-
Respiratory		
Bronchitis	1 to 4	-
Cough	≤3	✔
Dyspnea	1 to 6	1
Pharyngitis	2 to 6	-
Rhinitis	<10	-
Sinus congestion	1 to 2	-
Other		
Abnormal visual accommodation	-	<1
Allergic reaction	<2	-
Amblyopia	<2	-
Amnesia	<2	-
Blurred vision	-	<1
Flu-like syndrome	-	4
Parkinsonian syndrome	-	✔

Adverse Events	Diltiazem	Verapamil
Tinnitus	-	<1

✔ Percent not specified
- Event not reported

VII. Dosing and Administration

The usual dosing regimens for the miscellaneous calcium-channel blocking agents are listed in Table 7.

Table 7. Usual Dosing Regimens for the Calcium-Channel Blocking Agents, Miscellaneous[1,2,5-12]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Diltiazem	Angina pectoris (chronic stable): Extended-release capsule: initial, 120 mg/day; maintenance, 180 to 480 mg/day; maximum, 480 mg/day Extended-release tablet: initial, 180 mg once daily; maximum, 360 mg/day Tablet: initial, 30 mg four times daily; maintenance, 180 to 360 mg/day Angina pectoris (due to coronary artery spasm): Extended-release capsule (Cardizem CD®): initial, 120 or 180 mg once daily; maintenance, adjust dosage to each patient's needs Tablet: initial, 30 mg four times daily; maintenance, 180 to 360 mg/day Arrhythmias: Injection: weight based dosing administered intravenously Hypertension: Extended-release capsule: initial, 180 to 240 mg once daily; maintenance, 180 to 480 mg/day; maximum, 540 mg/day Extended-release tablet: initial, 180 to 240 mg once daily; maintenance, 120 to 540 mg/day; maximum, 540 mg/day	Safety and efficacy in children have not been established.	Extended-release capsule: 60 mg 90 mg 120 mg 180 mg 240 mg 300 mg 360 mg 420 mg Extended-release tablet: 120 mg 180 mg 240 mg 300 mg 360 mg 420 mg Injection: 5 mg/mL 100 mg Tablet: 30 mg 60 mg 90 mg 120 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Verapamil	Angina pectoris (chronic stable, unstable, and vasospastic): Tablet: maintenance, 80 to 120 mg three times a day Arrhythmias: Injection: weight based dosing administered by slow intravenous injection Tablet: maintenance, 240 to 480 mg/day, divided (three to four times daily) Hypertension: Tablet: initial, 80 mg three times daily; maintenance, 360 to 480 mg/day divided (three to four times daily); maximum, 480 mg/day Extended-release tablet: maintenance, 180 to 480 mg/day	Safety and efficacy of oral verapamil in children have not been established. Arrhythmias in children 0 to 15 years of age: Injection: weight based dosing administered by slow intravenous injection	Extended-release capsule 100 mg 120 mg 180 mg 200 mg 240 mg 300 mg 360 mg Extended-release tablet: 120 mg 180 mg 240 mg Injection: 2.5 mg/mL Tablet: 40 mg 80 mg 120 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the miscellaneous calcium-channel blocking agents are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Calcium-Channel Blocking Agents, Miscellaneous

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Angina				
De Rosa et al.[35] (1998) Diltiazem SR 300 mg QD vs verapamil SR 240 mg QD	DB, XO Men and women 48 to 72 years of age, with stable exertional angina, a positive test for myocardial ischemia and documented coronary artery disease	N=20 12 weeks	Primary: Exercise tolerance test: time to onset of angina, time to 1-mm ST-segment depression and total exercise duration Secondary: Heart rate, angina frequency, nitroglycerin use and adverse events	Primary: Time to onset of angina increased significantly in both groups compared to the placebo group (verapamil vs placebo; P<0.05 and diltiazem vs placebo; P<0.005). Time to 1-mm ST-segment depression increased significantly in both groups compared to the placebo group (verapamil vs placebo; P<0.05 and diltiazem vs placebo; P<0.005). Total exercise duration increased significantly in both groups compared to the placebo group (verapamil vs placebo; P<0.05 and diltiazem vs placebo; P<0.005). For each primary endpoint, there was no significant difference between the treatment groups. Secondary: Heart rates were similar between the treatment groups, except resting heart rate was significantly lower in the diltiazem group as compared to the verapamil group (68.5 vs 75.9; P<0.05). Angina frequency and nitroglycerin use decreased significantly in the diltiazem group compared to the placebo group (P<0.05) and to the verapamil group (P<0.05). Edema and flushing were most frequently reported. Similar rates of adverse events were reported for both treatments.
Chugh et al.[36] (2001) Diltiazem 240 mg	DB, DD, PG, RCT Patients with stable angina, blood	N=67 4 weeks	Primary: Treadmill exercise test: time to onset of angina, time to	Primary: Both treatment groups, and all doses, had significant increases in time to onset of angina from baseline (P<0.001 for all). There was no significant difference between the treatment groups (P=0.838) and between dose

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD for 2 weeks then 360 mg QD for 2 weeks vs amlodipine 5 mg QD for 2 weeks then 10 mg QD for 2 weeks	pressure in the range of 100/60 to 170/110 mm Hg and a positive ischemic response on a treadmill test, history of angiography		1-mm ST-segment depression Secondary: Heart rate, blood pressure, number of angina episodes and use of nitrates	levels (P=0.144) in time to onset of angina. Both treatment groups, and all doses, had significant increases in time to 1-mm ST-segment depression from baseline, except the low-dose amlodipine group (P<0.004, except P=0.063). There was no significant difference between the treatment groups and between dose levels (P=0.114) in time to 1-mm ST-segment depression (P=0.691). Secondary: There was no significant difference between the groups in heart rate at rest or maximal exercise. There was no significant difference between the groups in blood pressure at rest or maximal exercise, except SBP at rest was higher in the diltiazem group (137 to 143 vs 129 to 135 mm Hg; P=0.029). Both treatments reduced the number of angina episodes and the use of nitrates, but these results were not statistically different between the groups (P value not reported).
Van Kesteren et al.[37] (1998) Diltiazem CR 90 to 120 mg BID vs amlodipine 5 to 10 mg QD	DB, MC Men and women 41 to 77 years of age with a history of stable angina pectoris, a positive exercise tolerance test, and positive thallium scan or positive coronary angiogram	N=132 8 weeks	Primary: Exercise tolerance test: time to 1-mm ST-segment depression, time to onset of chest pain, time to end of exercise (exercise duration) Secondary: Safety	Primary: Diltiazem and amlodipine treatment resulted in significant increases in time to 1-mm ST-segment depression as compared to baseline (P<0.0001). Treatments were not significantly different from each other (P>0.05). Diltiazem and amlodipine treatment resulted in significant increases in time to onset of chest pain at four and eight weeks, (10 and 13% for amlodipine; P<0.0001; 5 and 7% for diltiazem; P=0.009). Treatments were not significantly different from each other (P>0.05). Amlodipine treatment resulted in a significant increase in total exercise duration as compared to baseline (P=0.0002), however the change from baseline for diltiazem was not significantly increased (P=0.43). There was no significant difference between the treatment groups at endpoint. Secondary: Ten patients (15.2%) in the amlodipine group and 17 patients (25.8%) in the diltiazem group reported an adverse event; two patients from the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				amlodipine group and six patients from the diltiazem group subsequently withdrew from the study.
Frishman et al.[38] (1999) Diltiazem 240 to 480 mg at bedtime vs amlodipine 5 to 10 mg QD vs amlodipine 5 to 10 mg QD plus atenolol 50 mg QD vs placebo	DB, MC, PC, PG, RCT Patients 30 to 80 years of age with chronic stable angina pectoris, evidence of exercise-induced ST-segment depression ≥1 mm and other evidence of cardiac disease	N=551 4 week	Primary: Exercise tolerance test (symptom-limited exercise duration, time ≥1-mm ST-segment depression and time to moderate angina) Secondary: 48-hour Holter-determined number of ischemic episodes, mean and total duration of ischemia, maximal depth of ST depression, heart rate at onset of ischemia	Primary: Treatment with verapamil, amlodipine, and amlodipine plus atenolol resulted in significantly better results than patients treated with placebo in: symptom-limited exercise duration, time ≥1-mm ST-segment depression and time to moderate angina (P≤0.01 for all vs placebo). Secondary: Treatment with verapamil, amlodipine, and amlodipine plus atenolol resulted in significantly fewer ischemic episodes in 48-hour Holter monitoring (P=0.003 for verapamil vs placebo). Treatment with amlodipine monotherapy resulted in a significant increase in duration of ischemic episode (P≤0.05 vs verapamil vs amlodipine plus atenolol and vs placebo). Treatment with verapamil and amlodipine plus atenolol resulted in a decrease in duration of ischemic episodes as compared to treatment with amlodipine and placebo (P≤0.05 for each). Heart rate at the onset of ischemic episode was significantly lower in the verapamil group and in the amlodipine plus atenolol group (P≤0.05 vs amlodipine) and higher in the amlodipine group (P≤0.05 vs verapamil, vs amlodipine plus atenolol and vs placebo).
Hauf-Zachariou et al.[39] (1997) Verapamil 120 mg TID vs carvedilol 25 mg BID	DB, MC, PG, RCT Patients 18 to 75 years with a confirmed diagnosis of CAD, exertional chest pain relieved by rest or glyceryl trinitrate for ≥2 months and 2 exercise tests with signs and symptoms	N=313 12 weeks	Primary: Total exercise time, time to onset of angina, and time to 1 mm ST-segment depression, blood pressure, heart rate, rate pressure product Secondary:	Primary: There was not a significant difference in total exercise time observed between the carvedilol (increased from 378 s to 436 s) and verapamil (increased from 386 s to 438 s) groups (RR, 1.14; 90% CI, 0.85±1.52). There was not a significant difference observed between the carvedilol and verapamil groups in time to onset of angina (increase from 296 s to 325 s vs 285 s to 326 s) and in time to 1 mm ST-segment depression (increase from 267 s to 298 s vs 286 s to 302 s). At peak exercise and at maximum comparable workload, carvedilol significantly reduced SBP (from 175 to 166 mm Hg) compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	of ischemia		Not reported	verapamil (from 173 to 173 mm Hg)). At peak exercise and at maximum comparable workload, carvedilol significantly reduced heart rate (from 123 to 112 mm Hg) compared to verapamil (from 124 to 120 mm Hg)). At peak exercise and at maximum comparable workload, carvedilol significantly reduced rate pressure product (from 21564 to 18802 mm Hg) compared to verapamil (from 21488 to 20992 mm Hg)). Secondary: Not reported
Cardiovascular Outcomes				
Boden et al.[40] (2002) INTERCEPT Diltiazem 300 mg QD vs placebo	DB, MC, PG, PRO, RCT Patients 75 years of age and younger, with acute MI, without CHF and who received a thrombolytic agent	N=874 Up to 6 months	Primary: Composite first-event rate of: cardiac death, nonfatal reinfarction or refractory ischemia Secondary: Composite of first occurrence of cardiac death, nonfatal reinfarction, recurrent ischemia, composite of cardiac death, nonfatal reinfarction, need for myocardial revascularization, safety	Primary: There was no significant difference between diltiazem treatment and placebo treatment in composite event rate (131 primary outcome events occurred in the placebo group and 97 occurred in the diltiazem group; P=0.07). Secondary: Rates of all composite nonfatal cardiac events (nonfatal reinfarction combined with refractory ischemia or all recurrent ischemia or need for revascularization) significantly favored the diltiazem group over the placebo group (P=0.05, P=0.05, P=0.03 respectively). Rates of cardiac death, nonfatal reinfarction, refractory ischemia and all recurrent ischemia were similar between the diltiazem group and the placebo group, however the need for revascularization favored the diltiazem group (P=0.67, P=0.47, P=0.07, P=0.07, P=0.03). There was no increase in rates of CHF, bleeding, cancer or cerebrovascular accidents in the diltiazem group.
Gibson et al.[41] (2000)	RETRO combined subgroup analysis	N=817	Primary: All cause mortality	Primary: Patients receiving treatment (either agent) had a 42% lower mortality rate

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Diltiazem 60 mg QID or verapamil 120 mg TID vs placebo	of 2 RCT Patients suffering acute non-Q-wave MI	12 to 18 months	Secondary: Combined cardiac events	than those receiving placebo (P=0.010). Secondary: Patients receiving treatment (either agent) had a 31% lower event rate (death or recurrent MI) than those receiving placebo (P<0.006).
Hansson et al.[42] (2000) NORDIL Diltiazem 180 to 360 mg QD vs conventional therapy (diuretic, β-blocker or both)	BE, MC, OL, PRO, RCT Patients 50 to 74 years of age with DBP ≥100 mm Hg and previously untreated	N=10,881 4.5 years	Primary: Combined fatal and nonfatal stroke, fatal and nonfatal MI, other cardiovascular death Secondary: Fatal plus nonfatal stroke and fatal plus nonfatal MI	Primary: The primary endpoint occurred in 403 of the diltiazem patients and 400 of the diuretic/β-blocker patients (RR, 1.00; 95% CI, 0.87 to 1.15; P=0.97). Secondary: Rates of secondary endpoints were similar between the groups. Fatal plus nonfatal stroke occurred in 159 of the diltiazem patients and 196 of the diuretic/β-blocker patients (P=0.04). Fatal plus nonfatal MI occurred in 183 of the diltiazem patients and 157 of the diuretic/β-blocker patients (P=0.17). Other endpoints were not statistically different between the groups including cardiovascular death (P=0.41), all cardiac events (P=0.57 and congestive heart failure (P=0.42).
Pepine et al.[43] (2003) INVEST Verapamil SR 240 mg/day (step 1), then add trandolapril if needed (step 2), then increase doses of both (step 3), then add HCTZ (step 4) (calcium antagonist	MC, OL, RCT Patients with essential HTN	N=22,576 24 months	Primary: First occurrence of death (all cause), nonfatal MI or stroke Secondary: Cardiovascular death, angina, cardiovascular hospitalization, angina, blood pressure control (SBP/DBP	Primary: At 24 months, in the calcium antagonist strategy subgroup, 81.5% of patients were taking verapamil SR, 62.9% trandolapril, and 43.7% HCTZ. In the non-calcium antagonist strategy, 77.5% of patients were taking atenolol, 60.3% HCTZ, and 52.4% trandolapril. After a follow-up of 61,835 patient-years (mean, 2.7 years per patient), 2,269 patients had a primary outcome event with no statistically significant difference between treatment strategies (9.93% in calcium antagonist strategy vs 10.17% in non-calcium antagonist strategy; RR, 0.98; 95% CI, 0.90 to 16; P=0.57). Secondary: There was no significant difference in the rate of cardiovascular death

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
strategy) vs atenolol 50 mg/day (step 1), then add HCTZ if needed (step 2), then increase doses of both (step 3), then add trandolapril (step 4) (non-calcium antagonist strategy) Trandolapril was recommended for all patients with heart failure, diabetes, or renal insufficiency.			<140/90 mm Hg or <130/85 mm Hg if diabetic or renal impairment), safety	(P=0.94) or cardiovascular hospitalization (P=0.59) between the two treatment groups. At 24 months, angina episodes decreased in both groups, but the mean frequency was lower in the calcium antagonist strategy group (0.77 episodes/week) compared to the non-calcium antagonist strategy group (0.88 episodes/week; P=0.02). Two-year blood pressure control was similar between groups. The blood pressure goals were achieved by 65.0% (systolic) and 88.5% (diastolic) of calcium antagonist strategy patients and 64.0% (systolic) and 88.1% (diastolic) of non-calcium antagonist strategy patients. A total of 71.7% of calcium antagonist strategy patients and 70.7% of non-calcium antagonist strategy patients achieved an SBP <140 mm Hg and DBP <90 mm Hg. Both regimens were generally well tolerated. Patients in the calcium antagonist strategy group reported constipation and cough more frequently than patients in the non-calcium antagonist strategy group, while non-calcium antagonist strategy patients experienced more dyspnea, lightheadedness, symptomatic bradycardia and wheezing (all were statistically significant with P≤0.05).
Mancia et al.[44] (2007) INVEST Verapamil SR 120 to 480 mg QD vs atenolol 25 to 200 mg QD	MC, open blinded endpoint, PRO, RCT Patients with HTN, requiring drug therapy (BP>140/90 or >130/80 mm Hg if diabetic or with renal impairment), and CAD	N=22,576 24 months	Primary: Occurrence of death, nonfatal MI and nonfatal stroke Secondary: Blood pressure control rates	Primary: Rates (death, nonfatal MI and nonfatal stroke) were similar for both treatment groups (P value not reported). Secondary: Rates of death, MI and stoke declined as the number of office visits for which blood pressure was controlled increased (P<0.001).
Pepine et al.[45] (2006) INVEST	Post hoc analysis of INVEST	N=22,576 24 months	Primary: Risk for adverse outcome associated	Primary: Previous heart failure (adjusted HR, 1.96), as well as diabetes (HR, 1.77), increased age (HR, 1.63), United States residency (HR, 1.61), renal

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Verapamil SR (step 1), then add trandolapril if needed (step 2), then increase doses of both (step 3), then add HCTZ (step 4) (calcium antagonist strategy) vs atenolol (step 1), then add HCTZ if needed (step 2), then increase doses of both (step 3), then add trandolapril (step 4) (non-calcium antagonist strategy)	Patients with essential HTN		with baseline factors, follow-up blood pressure and drug treatments Secondary: Not reported	impairment (HR, 1.50), stroke/TIA (HR, 1.43), smoking (HR, 1.41), MI (HR, 1.34), PVD (HR, 1.27), and revascularization (HR, 1.15) predicted increased risk. Follow-up SBP <140 mm Hg (HR, 0.82) or DBP <90 mm Hg (HR, 0.70) and trandolapril with verapamil SR (HR, 0.78 and 0.79) were associated with reduced risk. Secondary: Not reported
Bangalore et al.[46] (2008) INVEST Verapamil SR 120 to 480 mg QD vs atenolol 25 to 200 mg QD Trandolapril	INVEST substudy Patients 50 years of age and older with hypertension requiring drug therapy (blood pressure >140/90 or >130/80 mm Hg if diabetic or with renal impairment), and documented coronary artery	N=22,576 24 months	Primary: First occurrence of death, nonfatal MI, nonfatal stroke Secondary: Death, total MI, total stroke	Primary: No significant difference was observed between groups in the primary endpoint (P=0.30). Among patients with the primary outcome, no significant difference was observed between groups in the risk of death (P=0.94). There was no significant difference between groups in the risk of nonfatal MI (P=0.41). There was a trend toward a 29% reduction in the risk of nonfatal stroke in the verapamil group compared to the atenolol group (P=0.06).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
and/or HCTZ were added to control blood pressure.	disease			Secondary: The risks of fatal and nonfatal MI were similar between groups. No significant differences were observed between groups in fatal and nonfatal stroke (P=0.18).
Brunner et al.[47] (2007) INVEST Verapamil SR 240 mg and trandolapril 1 to 4 mg	Post hoc analysis of INVEST Patients with essential HTN	N=1,832 24 months	Primary: Factors influencing blood pressure response to trandolapril add-on therapy Secondary: Not reported	Primary: Trandolapril decreased mean unadjusted SBP and DBP by -9.1 and -4.1 mm Hg, respectively. The percentage of patients with blood pressure under control (<140/90 mm Hg) increased from 6.7 to 41.3% (P<0.0001). Adjusted blood pressure response was significantly associated with age and baseline SBP and DBP (P<0.0001). Whereas the decrease in SBP was more pronounced in younger patients, the opposite was observed for DBP decrease. DBP response was significantly associated with race. Specifically, the adjusted DBP decrease was significantly smaller in Hispanics and African Americans than whites (P=0.0032 and P=0.0069, respectively). However, Hispanics achieved a decrease in SBP and an increase in blood pressure control similar to the other ethnic groups. Secondary: Not reported
Black et al.[48] (2003) CONVINCE Verapamil ER 180 mg QD vs atenolol 50 mg QD vs HCTZ 12.5 mg	AC, DB, MC, RCT Patients 55 years of age and older with HTN and ≥1 risk factor for cardiovascular disease	N=16,476 3 years	Primary: Composite first occurrence of acute MI, stroke or cardiovascular disease-related death Secondary: Cardiovascular endpoints expanded, all-cause mortality, cancer,	Primary: There was no significant difference between the verapamil treatment group and the atenolol or HCTZ treatment groups in the composite primary endpoint (HR, 1.02; 95% CI, 0.88 to 1.18; P=0.77). Secondary: There was no significant difference between the verapamil treatment group and the atenolol or HCTZ treatment group in rates of cardiovascular-related hospitalization (P=0.31), death (all-cause mortality) (P=0.32) and cancer rates (P=0.46). Patients treated with verapamil experienced a significantly higher rate of death or bleeding unrelated to stroke (HR, 1.54; 95% CI, 1.15 to 2.04; P=0.003).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD			hospitalization for bleeding, incidence of primary endpoints between 6AM and noon, adverse events	Primary endpoints did not differ significantly based on time of day (P=0.43). Patients treated with verapamil were more likely to withdraw for adverse events or symptoms than those treated with atenolol or HCTZ (P=0.02).
Lindholm et al.[49] (2005) Other antihypertensive therapies (amiloride, amlodipine, bendro-flumethiazide*, captopril, diltiazem, enalapril, felodipine, HCTZ, isradipine, lacidipine, lisinopril, losartan, or verapamil) or placebo vs β-blocker therapy (atenolol, metoprolol, oxprenolol*, pindolol, or propranolol)	MA 13 RCTs evaluating the treatment of primary HTN with a β-blocker as first-line treatment (in ≥50% of all patients in one treatment group) and outcome data for all-cause mortality, cardiovascular morbidity or both	N=105,951 2.1 to 10.0 years	Primary: Stroke, MI, all-cause mortality Secondary: Not reported	Primary: The RR of stroke was 16% higher with β-blocker therapy than for the comparator therapies (RR, 1.16; 95% CI, 1.04 to 1.30; P=0.009). The RR of stroke was the highest with atenolol (26% higher) compared to other non β-blockers (RR, 1.26%; 95% CI, 15 to 38; P<0.0001). The relative risk of MI was 2% higher for β- blocker therapy than for the comparator therapies (RR, 1.02; 95% CI, 0.93 to 1.12), which was not significant (P value not reported). The RR of all-cause mortality was 3% higher for β-blocker therapy than for the comparator therapies (RR, 1.16; 95% CI, 0.99 to 1.08; P=0.14). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Wiysonge et al.[50] (2007) Other antihypertensive therapies (i.e., placebo, diuretics, calcium channel blockers, or renin-angiotensin system inhibitors) vs β-blockers (atenolol, metoprolol, oxprenolol*, or propranolol)	MA 13 RCTs evaluating patients ≥18 years of age with HTN	N=91,561 Duration varied	Primary: All-cause mortality Secondary: Stroke, CHD, cardiovascular death, total cardiovascular disease, adverse reactions	Primary: There was not a significant difference observed in all-cause mortality between β-blocker therapy and placebo (RR, 0.99; 95% CI, 0.88 to 1.11; P value not reported), diuretics (RR, 1.04; 95% CI, 0.91 to 1.19; P value not reported) or renin-angiotensin system inhibitors (RR, 1.10; 95% CI, 0.98 to 1.24; P value not reported). There was a significantly higher rate in all-cause mortality with β-blocker therapy compared to calcium channel blockers (RR, 1.07; 95% CI, 1.00 to 1.14; P=0.04). Secondary: There was a significant decrease in stroke observed with β-blocker therapy compared to placebo (RR, 0.80; 95% CI, 0.66 to 0.96). Also there was a significant increase in stroke with β-blocker therapy compared to calcium channel blockers (RR, 1.24; 95% CI, 1.11 to 1.40) and renin-angiotensin system inhibitors (RR, 1.30; 95% CI, 1.11 to 1.53), but there was no difference observed compared to diuretics (RR, 1.17; 95% CI, 0.65 to 2.09). CHD risk was not significantly different between β-blocker therapy and placebo (RR, 0.93; 95% CI, 0.81 to 1.07]), diuretics (RR, 1.12; 95% CI, 0.82 to 1.54), calcium channel blockers (RR, 1.05; 95% CI, 0.96 to 1.15) or renin-angiotensin system inhibitors (RR, 0.90; 95% CI, 0.76 to 1.06). The risk of total cardiovascular disease was lower with β-blocker therapy compared to placebo (RR, 0.88; 95% CI, 0.79 to 0.97). The effect of β-blocker therapy on cardiovascular disease was significantly worse than that of calcium channel blockers (RR, 1.18; 95% CI, 1.08 to 1.29), but was not significantly different from that of diuretics (RR, 1.13; 95% CI, 0.99 to 1.28) or renin-angiotensin system inhibitors (RR, 1.00; 95% CI, 0.72 to 1.3). There was a significantly higher rate of discontinuation due to side effects with β-blocker therapy compared to diuretics (RR, 1.86; 95% CI, 1.39 to 2.50) and renin-angiotensin system inhibitors (RR, 1.41; 95% CI, 1.29 to 1.54), but there was no significant difference compared to calcium channel blockers (RR, 1.20; 95% CI, 0.71 to 2.04). Actual side effects were not reported.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Hypertension				
Wright et al.[51] (2004) Diltiazem graded-release 360 to 540 mg QD vs amlodipine 5 to 10 mg QD	AC, DB, MC, PG, RCT Male and female African Americans patients 18 to 80 years of age with hypertension (DBP 85 to 109 mm Hg and SBP <180 mm Hg)	N=268 12 weeks	Primary: Change from baseline in DBP during first 4 hours of awakening as recorded by ambulatory blood pressure monitoring Secondary: Changes from baseline in BP, heart rate, rate-pressure product, safety	Primary: Reductions in DBP during the first four hours after awakening, and from 6AM to noon, were significantly greater in the diltiazem group than in the amlodipine group (-13.12 vs -9.65 mm Hg; P=0.0049 and -11.97 vs -8.75 mm Hg; P=0.0019). Secondary: Reductions in SBP during the first four hours after awakening and between 6AM and noon, were similar between the groups (P<0.0768 and P<0.9470). Mean 24-hour SBP reductions were significantly greater in the amlodipine group than in the diltiazem group (-14.08 vs -10.64; P=0.0022). Reductions in heart rate were significantly greater in the diltiazem group than in the amlodipine group (24 hour mean: -4.88 vs 1.77; P<0.0001). Reductions in rate-pressure product were significantly greater in the diltiazem group than in the amlodipine group (24 hour mean: -1,493 vs –881; P<0.0008). In the diltiazem and amlodipine groups respectively, 1.5 and 2.2% discontinued early due to adverse events.
White et al.[52] (2004) Diltiazem ER 240 to 540 mg at bedtime vs ramipril 5 to 20 mg at bedtime	DB, MC, PG, RCT Men and women, with hypertension: DBP 90 to 110 mm Hg	N=261 10 weeks	Primary: Change in early morning DBP from baseline Secondary: Change in SBP from baseline, heart rate, heart rate × systolic blood pressure product, 24-hr ambulatory	Primary: Changes in early morning DBP were significantly larger in the diltiazem group than in the ramipril group (-15 vs -8 mm Hg; P<0.001). Secondary: Changes in early morning SBP were significantly larger in the diltiazem group than in the ramipril group (-18 vs -13 mm Hg; P=0.002). Decreases in heart rate and heart-rate systolic BP product were significantly larger in the diltiazem group than in the ramipril group (-8.9 vs -2.7 beats/min; P<0.0001 and -2518 vs -1393; P<0.0001). Reductions in DBP and heart rate and increases in the rate-pressure

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			monitoring, safety	product measured by 24-hr ambulatory monitoring and clinic monitoring were significantly greater for diltiazem than for ramipril (P<0.0001 for all). 50% of diltiazem patients and 40% of ramipril patients reported experiencing any adverse event; edema and cough respectively were most frequently reported for each treatment. Withdrawal rates from the study were low and similar between the groups.
Rosei et al.[53] (1997) VHAS Verapamil SR 240 mg QD vs chlorthalidone 25 mg QD	DB (1st 6 months), MC, PG, RCT Patients 40 to 65 years of age, with HTN (SBP ≥160 mm Hg and DBP ≥95 mm Hg)	N=1,414 2 years	Primary: Blood pressure Secondary: Cardiovascular events, adverse events	Primary: Both treatments significantly reduced SBP and DBP compared to baseline, however reductions did not significantly differ between treatments (verapamil reduction, 27.6/17.0 mm Hg vs chlorthalidone reduction, 28.6/16.6 mm Hg; P<0.01 for each vs baseline). Goal DBP was achieved in 69.3% of patients receiving verapamil and 66.9% of patients receiving chlorthalidone (P value not reported). Secondary: Serum TC levels and heart rate decreased significantly in the verapamil group as compared to baseline and the chlorthalidone group (TC; P<0.01 for both, heart rate; P<0.05). The number of nonfatal cardiovascular events was similar between the groups, 37 in the verapamil group and 39 in the chlorthalidone group (P value not reported). The number of cardiovascular deaths was similar between the groups, five in the verapamil group and four in the chlorthalidone group (P value not reported). Hypokalemia and hyperuricemia occurred significantly more frequently in the chlorthalidone group than in the verapamil group (P<0.01 for both). Two hundred and thirty six patients reported 403 adverse events in the chlorthalidone group and 230 patients reported 387 adverse events in the verapamil group. Asthenia was the most commonly reported adverse event in the chlorthalidone group and constipation was the most commonly

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				reported adverse event in the verapamil group.
Ruggenenti et al.[54] (2004) BENEDICT Trandolapril 2 mg/day vs verapamil SR 240 mg/day vs trandolapril and verapamil SR 2-180 mg/day (fixed-dose combination) vs placebo	DB, MC, RCT Patients ≥40 years with type 2 diabetes (not exceeding 25 years) and HTN (SBP ≥130 mm Hg and/or DBP ≥85 mm Hg) but with normoalbuminuria (urinary albumin excretion rate of <20 mcg/minute)	N=1,204 3.6 years (median)	Primary: Development of persistent microalbuminuria comparing combination therapy to placebo, acceleration factor Secondary: Primary end point comparing trandolapril and verapamil monotherapy to placebo, blood pressure, adverse events	Primary: The primary outcome was reached in 5.7% of patients receiving combination therapy vs 10.0% for patients receiving placebo. The estimated acceleration factor (which quantifies the effect of one treatment relative to another in accelerating or slowing disease progression) adjusted for predefined baseline characteristics was 0.39 for the comparison between verapamil plus trandolapril and placebo (P=0.01). Secondary: The primary outcome was reached in 6.0% of patients receiving trandolapril, 11.9% receiving verapamil, and 10.0% receiving placebo. The estimated acceleration factor was 0.47 for trandolapril vs placebo (P=0.01) and 0.83 for verapamil vs placebo (P=0.54). Trandolapril plus verapamil and trandolapril alone delayed the onset of microalbuminuria by factors of 2.6 and 2.1, respectively. Throughout the study the average trough SBP/DBP was 139/80 mm Hg for patients receiving trandolapril plus verapamil, 139/81 mm Hg for trandolapril, 141/82 mm Hg for verapamil and 142/83 mm Hg for placebo. The comparison was significant (P≤0.002) between trandolapril plus verapamil or trandolapril alone vs placebo, but not for verapamil vs placebo. Serious adverse events were similar in all treatment groups.
Messerli et al.[55] (2006) Verapamil SR 240 mg QD vs trandolapril 4 mg QD	DB, MC, PC, PG, RCT Patients, 21 years old and older with DBP of 95 to 114 mm Hg	N=581 6 weeks	Primary: Blood pressure Secondary: Not reported	Primary: All 3 treatment groups had significant blood pressure reductions from baseline (P<0.01 for all). Patients receiving the combination of trandolapril and verapamil had significantly greater reductions in blood pressure as compared to patients receiving trandolapril or verapamil alone (P<0.01 for both comparisons). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs verapamil SR 240 mg and trandolapril 4 mg QD (separate entities)				
Karlberg et al.[56] (2000) Trandolapril 2 mg/day vs verapamil 240 mg/day vs trandolapril and verapamil 2-180 mg/day (fixed-dose combination)	DB, MC, PRO, RCT, XO Patients with uncomplicated primary HTN (sitting DBP between 95 and 115 mm Hg) between the ages of 20 to 80 years	N=226 2 months	Primary: Change in blood pressure and rate pressure product Secondary: Predictive value of plasma concentrations of active renin regarding the blood pressure response to the different treatment regimens, safety	Primary: The mean fall in blood pressure was significantly greater with the combination (20/15 mm Hg; P<0.00054), as compared to trandolapril (14/11 mm Hg) or verapamil (13/11) mm Hg. The difference between verapamil and trandolapril was not significant. Rate pressure product decreased significantly more on the combination (P<0.001) than on trandolapril or verapamil alone. Secondary: There was a significant positive correlation between blood pressure fall and plasma concentrations of active renin (e.g., the higher the initial active renin, the better the blood pressure response to trandolapril [P<0.045 for SBP and P<0.004 for DBP]). No relationships were found for either verapamil or the combination. All treatments were well tolerated and safe.
Van Bortel et al.[57] (2008) ACE inhibitor, ARB, β-blocker, calcium channel blocker, or placebo vs nebivolol	MA 12 RCTs involving >25 patients with essential HTN where nebivolol 5 mg QD was compared to placebo or other active drugs for >1 month	N=2,653 Duration varied	Primary: Antihypertensive effect and tolerability Secondary: Not reported	Primary: Overall, higher response rates were observed with nebivolol than all other antihypertensive agents combined (OR, 1.41; 95% CI, 1.15 to 1.73; P=0.001) and compared to the ACE inhibitors (OR, 1.92; 1.30 to 2.85; P=0.001), but response rates to nebivolol were similar to β-blockers (OR, 1.29; 95% CI, 0.81 to 2.04; P=0.283), calcium channel blockers (OR, 1.19; 95% CI, 0.83 to 1.70; P=0.350) and losartan (OR, 1.35; 95% CI, 0.84 to 2.15; P=0.212). Overall, a higher percentage of patients obtained normalized blood pressure with nebivolol compared to the other antihypertensive agents combined (OR, 1.35; 95% CI, 1.07 to 1.72; P=0.012). A higher percentage

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				of patient receiving nebivolol obtained normalized blood pressure compared to losartan (OR, 1.98; 95% CI, 1.24 to 3.15; P=0.004) and calcium channel blockers (OR, 1.96; 95% CI, 1.05 to 1.96; P=0.024), but not when compared to other β-blockers (OR, 1.29; 95% CI, 0.81 to 1.65; P=0.473). Overall, the percentage of adverse events was significantly lower with nebivolol compared to the other antihypertensive agents combined (OR, 0.59; 95% CI, 0.48 to 0.72; P<0.001) and similar to placebo (OR, 1.16; 95% CI, 0.76 to 1.67; P=0.482). In comparing nebivolol to the individual treatments, nebivolol had a lower percentage of adverse events compared to losartan (OR, 0.52; 95% CI, 0.30 to 0.89; P=0.016), the other β-blockers (OR, 0.56; 95% CI, 0.36 to 0.85; P=0.007) and calcium channel blockers (OR, 0.49; 95% CI 0.33 to 0.72; P<0.001), but was similar to ACE inhibitors (OR, 0.75; 95% CI 0.52 to 1.08). Secondary: Not reported
Hilleman et al.[58] (1999) Amlodipine-benazepril (fixed-dose combination) vs monotherapy (atenolol, HCTZ, captopril, enalapril, lisinopril, amlodipine, diltiazem, nifedipine, verapamil)	MA Patients with mild to moderate essential HTN	82 trials ≥4 weeks	Primary: Absolute change in supine DBP from baseline Secondary: Percent of patients who achieved blood pressure control, safety	Primary: The mean absolute decrease in supine DBP ranged from 9.7 to 13.3 mm Hg with verapamil showing the greatest effect and captopril the least. When studies were weighted by sample size, amlodipine and benazepril, atenolol, lisinopril, and verapamil showed the greatest blood pressure effect. Secondary: The average percentage of patients defined as controlled after treatment varied from 53.5 to 79.0%, with amlodipine and benazepril (74.3%) and lisinopril (79.0%) showing the highest percentage control (P=0.096). The incidence of adverse events ranged from 12.1 to 41.8%, with lisinopril and verapamil showing the lowest incidences (12.1% and 14.1%, respectively) and nifedipine the highest incidence. Lisinopril demonstrated significantly less overall side effects compared to nifedipine (P=0.030). Nifedipine demonstrated a higher withdrawal rate due to side effects compared to atenolol, HCTZ, enalapril, amlodipine, and diltiazem

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(P=0.002). Although amlodipine and benazepril had the lowest rate of withdrawals due to adverse events, lack of significant change was due to the low number of cohorts available for analysis.
Casas et al.[59] (2005) ACE inhibitor or ARBs compared to placebo vs ACE inhibitor or ARBs compared to other antihypertensive drugs (β-adrenergic blocking agents, α-adrenergic blocking agents, calcium-channel blocking agents, or combinations) Specific agents and doses were not specified.	MA (127 trials) Studies in adults that examined the effect of any drug treatment with a blood pressure lowering action on progression of renal disease	N=not reported 4.2 years (mean)	Primary: Doubling of serum creatinine, and ESRD Secondary: Serum creatinine, urine albumin excretion and GFR	Primary: Treatment with ACE inhibitors or ARBs resulted in a nonsignificant reduction in the risk of doubling of creatinine vs other antihypertensives (P=0.07) with no differences in the degree of change of SBP or DBP between the groups. A small reduction in ESRD was observed in patients receiving ACE inhibitors or ARBs compared to other antihypertensives (P=0.04) with no differences in the degree of change of SBP or DBP between the groups. Secondary: Small reductions in serum creatinine and in SBP were noted when ACE inhibitors or ARBs were compared to other antihypertensives (P=0.01). Small reduction in daily urinary albumin excretion in favor of ACE inhibitor or ARBs were reported when these agents were compared to other antihypertensives (P=0.001). Compared to other drugs, ACE inhibitors or ARBs had no effect on the GFR.
Miscellaneous				
Siu et al.[60] (2009) Diltiazem IV 0.25 mg/kg to 10 mg/kg vs	OL, RCT Patients who presented to the emergency room with symptomatic acute atrial fibrillation for <48	N=150 3 years	Primary: Sustained ventricular rate control (<bpm) within 24 hours Secondary: Time to ventricular	Primary: The time to ventricular control for the 45 patients assigned to diltiazem was achieved 90% of the time compared to digoxin (74%) and amiodarone (74%) (P<0.0001). Secondary: The median time to ventricular control was significantly shorter in the diltiazem group (3 hours, 1-21 hours) compared to the digoxin (6 hours, 3

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
digoxin IV 0.5 mg to 0.25 mg vs amiodarone IV 300 mg to 10 mg/kg	hours and rapid ventricular rate >120 bpm necessitating hospitalization		control, atrial fibrillation symptom improvement, hospital stay, and adverse events	to 15 hours, P<0.001) and amiodarone groups (7 hours, 1 to 18 hours, P=0.003). The diltiazem group had the largest reduction in atrial fibrillation frequency score and severity score (P<0.0001). Length of hospital stay was significantly shorter in the diltiazem group (3.9±1.6 days) compared to digoxin (4.7±2.1 days, P=0.023) and amiodarone groups (4.7±2.2 days, P=0.038).

*Agent not available in the United States.
Drug regimen abbreviations: BID=twice daily, CR=controlled-release, ER=extended-release, IV=intravenous, QD=once daily, SR=sustained-release, TID=three times daily
Study design abbreviations: AC=active comparator, BE=blinded endpoint, DB=double blind, DD=double dummy, MA=meta analysis, MC=multicenter, OL=open label, PC=placebo controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, XO=cross over
Miscellaneous abbreviations: ACE inhibitor=angiotensin converting enzyme inhibitor, ARB=angiotensin II receptor blocker, CAD=coronary artery disease, CHD=coronary heart disease, CHF=congestive heart failure, CI=confidence interval, DBP=diastolic blood pressure, ESRD=end stage renal disease, GFR=glomerular filtration rate, HCTZ=hydrochlorothiazide, HTN=hypertension, HR=hazard ratio, MI=myocardial infarction, OR=odds ratio, PVD=peripheral vascular disease, RR=relative risk, SBP=systolic blood pressure, TC=total cholesterol, TIA=transient ischemic attack

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 9. Relative Cost of the Calcium-Channel Blocking Agents, Miscellaneous

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Diltiazem	extended-release capsule, extended-release tablet, injection, tablet	Cardizem®*, Cardizem CD®*, Cardizem LA®, Matzim LA®, Tiazac ER®*	$$$	$
Verapamil	extended-release capsule, extended-release tablet, injection, tablet	Calan SR®*, Verelan®*, Verelan PM®*	$$$$ to $$$$$	$$

*Generic is available in at least one dosage form or strength.

X. Conclusions

The miscellaneous calcium-channel blocking agents are approved for the treatment of angina, arrhythmias and hypertension.[1,2,5-12] Diltiazem and verapamil are available in a variety of modified-release delivery systems that alter their pharmacokinetic properties, including onset and duration of action.[1,2] Both drugs are available in a generic formulation.

There are several national and international guidelines that provide recommendations regarding the use of calcium-channel blocking agents.[13-34] For the treatment of chronic angina, β-blockers are recommended as initial therapy; however, long-acting calcium-channel blocking agents may be used if β-blockers are contraindicated or if additional therapy is required.[13-18] Calcium-channel blocking agents are recommended as initial therapy in patients

with variant/vasospastic angina.[14,17] Verapamil may be considered for secondary prevention of cardiovascular disease in patients with no heart failure in whom β-blockers are contraindicated.[19] Treatment options for atrial fibrillation include ventricular rate control or drug therapy to maintain sinus rhythm. The AFFIRM, RACE, and HOT CAFE trials demonstrated similar outcomes with rate control compared to rhythm control strategies. β-blockers and nondihydropyridine calcium-channel blocking agents are recommended for patients with persistent or permanent atrial fibrillation, either alone or in combination with digoxin.[23-25] For the treatment of heart failure, ACE inhibitors, ARBs, aldosterone antagonists, and isosorbide dinitrate/hydralazine are recommended as initial therapy. In general, calcium-channel blocking agents are not recommended for the routine treatment of heart failure.[20-21] Thiazide-type diuretics are frequently recommended as initial therapy in patients with uncomplicated hypertension.[26-31] According to the National Heart, Lung, and Blood Institute's Eighth Report of The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8), thiazide-type diuretics should be utilized first-line for most patients with hypertension, either alone or in combination with another hypertensive from a different medication class (e.g., ACE inhibitors, ARBs, β-blockers, calcium channel blockers).[26] Several guidelines consistently recommend that the selection of an antihypertensive agent be based on compelling indications for use.[26-33] Most patients will require more than one antihypertensive medication to achieve blood pressure goals.[26-33]

Clinical trials demonstrate that diltiazem and verapamil can effectively treat angina and improve blood pressure.[35-39,51-59] Both agents have been shown to reduce mortality and cardiovascular event rates compared to placebo.[41] Evidence suggests that there is no overall difference between diltiazem and verapamil compared to other antihypertensive agents (β-blockers, atenolol, diuretics) in reducing cardiovascular events and mortality in patients with hypertension.[42-48]

There is insufficient evidence to support that one brand miscellaneous calcium-channel blocking agent is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand miscellaneous calcium-channel blocking agents within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand miscellaneous calcium-channel blocking agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Angiotensin-Converting Enzyme Inhibitors
AHFS Class 243204
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I. Overview

The renin-angiotensin-aldosterone system (RAAS) is the most important component in the homeostatic regulation of blood pressure. Excessive activity of the RAAS may lead to hypertension, as well as fluid and electrolyte disorders. Renin catalyzes the conversion of angiotensinogen to angiotensin I. Angiotensin I is then cleaved to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II may also be generated through other pathways (angiotensin I convertase). Angiotensin II can increase blood pressure by direct vasoconstriction, as well as through actions on the brain and autonomic nervous system. In addition, angiotensin II stimulates aldosterone synthesis from the adrenal cortex, leading to sodium and water reabsorption. Angiotensin II exerts other detrimental effects, which include ventricular hypertrophy and remodeling and myocyte apoptosis.[1-2]

The ACE inhibitors are approved for the treatment of diabetic nephropathy, heart failure, hypertension, and post-myocardial infarction.[3-18] They block the conversion of angiotensin I to angiotensin II, and also inhibit the breakdown of bradykinin, which is a potent vasodilator. However, this increase in bradykinin also leads to an increase in adverse effects, including cough.[3-18] The ACE inhibitors are available as single entity products, as well as in combination with hydrochlorothiazide. Hydrochlorothiazide inhibits the reabsorption of sodium and chloride in the cortical thick ascending limb of the loop of Henle and the early distal tubules. This action leads to an increase in the urinary excretion of sodium and chloride. [18,19]

The angiotensin-converting enzyme inhibitors that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All of the products are available in a generic formulation. This class was last reviewed in May 2022.

Table 1. Angiotensin-Converting Enzyme Inhibitors Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Benazepril	tablet	Lotensin®*	benazepril
Captopril	tablet	N/A	captopril
Enalapril	solution, tablet	Epaned®*, Vasotec®*	enalapril
Enalaprilat	injection^	N/A	enalaprilat dihydrate
Fosinopril	tablet	N/A	fosinopril
Lisinopril	solution, tablet	Prinivil®*, Qbrelis®, Zestril®*	lisinopril
Moexipril	tablet	N/A	moexipril
Perindopril	tablet	N/A	perindopril
Quinapril	tablet	Accupril®*	quinapril
Ramipril	capsule	Altace®*	ramipril
Trandolapril	tablet	N/A	trandolapril
Combination Products			
Benazepril and hydrochlorothiazide	tablet	Lotensin HCT®*	benazepril and hydrochlorothiazide
Captopril and hydrochlorothiazide	tablet	N/A	captopril and hydrochlorothiazide
Enalapril and hydrochlorothiazide	tablet	Vaseretic®*	enalapril and hydrochlorothiazide
Fosinopril and hydrochlorothiazide	tablet	N/A	fosinopril and hydrochlorothiazide
Lisinopril and hydrochlorothiazide	tablet	Prinzide®*, Zestoretic®*	lisinopril and hydrochlorothiazide

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Quinapril and hydrochlorothiazide	tablet	Accuretic®*	quinapril and hydrochlorothiazide

*Generic is available in at least one dosage form or strength.
^Product is primarily administered in an institution.
PDL=Preferred Drug List
N/A=Not available

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the angiotensin-converting enzyme inhibitors are summarized in Table 2.

Table 2. Treatment Guidelines Using the Angiotensin-Converting Enzyme Inhibitors

Clinical Guideline	Recommendations
American Heart Association/American College of Cardiology/American College of Clinical Pharmacy/American Society for Preventive Cardiology/National Lipid Association/ Preventive Cardiovascular Nurses Association **Guideline for the Management of Patients With Chronic Coronary Disease (2023)**[19]	• In patients with chronic coronary disease (CCD), high-intensity statin therapy is recommended with the aim of achieving a ≥50% reduction in LDL-C levels to reduce the risk of major adverse cardiovascular events (MACE). • In patients in whom high-intensity statin therapy is contraindicated or not tolerated, moderate-intensity statin therapy is recommended with the aim of achieving a 30% to 49% reduction in LDL-C levels to reduce the risk of MACE. • In patients with CCD who are judged to be at very high risk and on maximally tolerated statin therapy with an LDL-C level ≥70 mg/dL, ezetimibe can be beneficial to further reduce the risk of MACE. • In patients with CCD who are judged to be at very high risk and who have an LDL-C level ≥70 mg/dL, or a non–high-density lipoprotein cholesterol (HDL-C) level ≥100 mg/dL, on maximally tolerated statin and ezetimibe, a PCSK9 monoclonal antibody can be beneficial to further reduce the risk of MACE. • In patients with CCD on maximally tolerated statin therapy with an LDL-C level <100 mg/dL and a persistent fasting triglyceride level of 150 to 499 mg/dL after addressing secondary causes, icosapent ethyl may be considered to further reduce the risk of MACE and cardiovascular death. • In patients with CCD who are not at very high risk and on maximally tolerated statin therapy with an LDL-C level ≥70 mg/dL, it may be reasonable to add ezetimibe to further reduce the risk of MACE. • In patients with CCD on maximally tolerated statin therapy who have an LDL-C level ≥70 mg/dL, and in whom ezetimibe and PCSK9 monoclonal antibody are deemed insufficient or not tolerated, it may be reasonable to add bempedoic acid or inclisiran (in place of PCSK9 monoclonal antibody) to further reduce LDL-C levels. • In patients with CCD receiving statin therapy, adding niacin, fenofibrate, or dietary supplements containing omega-3 fatty acids are not beneficial in reducing cardiovascular risk. • In adults with CCD, nonpharmacologic strategies are recommended as first-line therapy to lower BP in those with elevated BP (120-129/<80 mmHg). • In adults with CCD who have hypertension, a BP target of <130/<80 mmHg is recommended to reduce CVD events and all-cause death. • In adults with CCD and hypertension (systolic BP ≥130 and/or diastolic BP ≥80 mm Hg), in addition to nonpharmacological strategies, GDMT angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), or beta blockers are recommended as first-line therapy for compelling indications (e.g., recent MI or angina), with additional antihypertensive medications (e.g., dihydropyridine calcium channel blockers [CCB], long-acting thiazide diuretics, and/or mineralocorticoid receptor antagonists) added as needed to optimize BP control. • In patients with CCD and no indication for oral anticoagulant therapy, low-dose

Clinical Guideline	Recommendations
	aspirin 81 mg (75 to 100 mg) is recommended to reduce atherosclerotic events. • In patients with CCD treated with PCI, dual antiplatelet therapy (DAPT) consisting of aspirin and clopidogrel for 6 months post PCI followed by single antiplatelet therapy (SAPT) is indicated to reduce MACE and bleeding events.* • In select patients with CCD treated with PCI and a drug-eluting stent (DES) who have completed a 1- to 3-month course of DAPT, P2Y12 inhibitor monotherapy for at least 12 months is reasonable to reduce bleeding risk. • In patients with CCD who have had a previous MI and are at low bleeding risk, extended DAPT beyond 12 months for a period of up to 3 years may be reasonable to reduce MACE. • In patients with CCD and a previous history of MI without a history of stroke, transient ischemic attack (TIA), or ICH, vorapaxar may be added to aspirin therapy to reduce MACE. • In patients with CCD, the use of DAPT after CABG may be useful to reduce the incidence of saphenous vein graft occlusion. • In patients with CCD without recent ACS or a PCI-related indication for DAPT, the addition of clopidogrel to aspirin therapy is not useful to reduce MACE. • In patients with CCD and previous stroke, TIA, or ICH, vorapaxar should not be added to DAPT because of increased risk of major bleeding and ICH. • In patients with CCD and previous stroke, TIA, or ICH, prasugrel should not be used because of risk of significant or fatal bleeding. • In patients with CCD, chronic nonsteroidal anti-inflammatory drugs should not be used because of increased cardiovascular and bleeding complications. • In patients with CCD who have undergone elective PCI and who require oral anticoagulant therapy, DAPT for one to four weeks followed by clopidogrel alone for six months should be administered in addition to DOAC. • In patients with CCD who have undergone PCI and who require oral anticoagulant therapy, continuing aspirin in addition to clopidogrel for up to 1 month is reasonable if the patient has a high thrombotic risk and low bleeding risk. • In patients with CCD who require oral anticoagulation and have a low atherothrombotic risk, discontinuation of aspirin therapy with continuation of DOAC alone may be considered one year after PCI to reduce bleeding risk. • In patients with CCD who require oral anticoagulation, DOAC monotherapy may be considered if there is no acute indication for concomitant antiplatelet therapy. • In patients with CCD without an indication for therapeutic DOAC or DAPT and who are at high risk of recurrent ischemic events but low-to-moderate bleeding risk, the addition of low-dose rivaroxaban 2.5 mg twice daily to aspirin 81 mg daily is reasonable for long-term reduction of risk for MACE. • In patients with CCD on DAPT, the use of a PPI can be effective in reducing gastrointestinal bleeding risk. • In patients with CCD and LVEF ≤40% with or without previous MI, the use of beta-blocker therapy is recommended to reduce the risk of future MACE, including cardiovascular death. • In patients with CCD and LVEF<50%, the use of sustained release metoprolol succinate, carvedilol, or bisoprolol with titration to target doses is recommended in preference to other beta blockers. • In patients with CCD who were initiated on beta-blocker therapy for previous MI without a history of or current LVEF ≤50%, angina, arrhythmias, or uncontrolled hypertension, it may be reasonable to reassess the indication for long-term (>1 year) use of beta-blocker therapy for reducing MACE. • In patients with CCD without previous MI or LVEF ≤50%, the use of beta-blocker therapy is not beneficial in reducing MACE, in the absence of another primary indication for beta-blocker therapy. • In patients with CCD who also have hypertension, diabetes, LVEF ≤40%, or

Clinical Guideline	Recommendations
	CKD, the use of ACE inhibitors, or ARBs if ACE inhibitor–intolerant, is recommended to reduce cardiovascular events. • In patients with CCD without hypertension, diabetes, or CKD and LVEF >40%, the use of ACE inhibitors or ARBs may be considered to reduce cardiovascular events. • In patients with CCD, the addition of colchicine for secondary prevention may be considered to reduce recurrent ASCVD events. • In patients with CCD, an annual influenza vaccination is recommended to reduce cardiovascular morbidity, cardiovascular death, and all-cause death. • In patients with CCD, coronavirus disease 2019 (COVID-19) vaccination is recommended per public health guidelines to reduce COVID-19 complications. • In patients with CCD, a pneumococcal vaccine is reasonable to reduce cardiovascular morbidity and mortality and all-cause death. • In patients with CCD and angina, antianginal therapy with either a beta blocker, CCB, or long-acting nitrate is recommended for relief of angina or equivalent symptoms. • In patients with CCD and angina who remain symptomatic after initial treatment, addition of a second antianginal agent from a different therapeutic class (beta blockers, CCB, long-acting nitrates) is recommended for relief of angina or equivalent symptoms. • In patients with CCD, ranolazine is recommended in patients who remain symptomatic despite treatment with beta blockers, CCB, or long-acting nitrate therapies. • In patients with CCD, sublingual nitroglycerin or nitroglycerin spray is recommended for immediate short-term relief of angina or equivalent symptoms. • In patients with CCD and normal LV function, the addition of ivabradine to standard anti-anginal therapy is potentially harmful. • In patients with CCD and lifestyle-limiting angina despite GDMT and with significant coronary artery stenoses amenable to revascularization, revascularization is recommended to improve symptoms. • In patients with CCD who have experienced SCAD, beta-blocker therapy may be reasonable to reduce the incidence of recurrent SCAD. • Women with CCD who are contemplating pregnancy or who are pregnant should not use ACE inhibitors, ARBs, direct renin inhibitors, angiotensin receptor-neprilysin inhibitors, or aldosterone antagonists during pregnancy to prevent harm to the fetus. • Women with CCD should not receive systemic postmenopausal hormone therapy because of a lack of benefit on MACE and mortality, and an increased risk of venous thromboembolism.
European Society of Cardiology: **Guidelines for the Diagnosis and Management of Chronic Coronary Syndromes (2019)**[20]	<u>Pharmacological management of stable coronary artery disease (CAD) patients</u> • The two aims of the pharmacological management of stable CAD patients are to obtain relief of symptoms and to prevent CV events. • Optimal medical treatment indicates at least one drug for angina/ischaemia relief plus drugs for event prevention. • It is recommended to educate patients about the disease, risk factors and treatment strategy. • It is indicated to review the patient's response soon after starting therapy. • Concomitant use of a proton pump inhibitor is recommended in patients receiving aspirin monotherapy, DAPT, or DOAC monotherapy who are at high risk of gastrointestinal bleeding. • Lipid-lowering drugs: if goals are not met on maximum tolerated dose of a statin, consideration of combination therapy with ezetimibe or a PCSK9 inhibitor is recommended • ACE inhibitors should be considered in patients at a very high risk of cardiovascular adverse events

Clinical Guideline	Recommendations

	• Angina/ischemia relief:
	  o Short-acting nitrates are recommended.
	  o First-line treatment is indicated with ß-blockers and/or calcium channel blockers to control heart rate and symptoms.
	  o Long-acting nitrates should be considered as a second-line treatment option when initial therapy with a beta-blocker and/or a non-DHP-calcium channel blocker is contraindicated, poorly tolerated, or inadequate in controlling angina symptoms
	  o Nicorandil, ranolazine, ivabradine, or trimetazidine should be considered as a second-line treatment to reduce angina frequency and improve exercise tolerance in subjects who cannot tolerate, have contraindications to, or whose symptoms are not adequately controlled by beta-blockers, CCBs, and long-acting nitrates.
	  o According to comorbidities/tolerance, it is indicated to use second-line therapies as first-line treatment in selected patients.
	  o In asymptomatic patients with large areas of ischaemia (>10%) ß-blockers should be considered.
	  o In patients with vasospastic angina, calcium channel blockers and nitrates should be considered and beta-blockers avoided.
	• Event prevention:
	  o Low-dose aspirin daily is recommended in all stable CAD patients.
	  o Clopidogrel is indicated as an alternative in case of aspirin intolerance.
	  o Statins are recommended in all stable CAD patients.
	  o It is recommended to use ACE inhibitors (or ARBs) if presence of other conditions (e.g., heart failure, hypertension or diabetes).
	
	<u>Treatment in patients with microvascular angina</u>
	• It is recommended that all patients receive secondary prevention medications including aspirin and statins.
	• ß-blockers are recommended as a first-line treatment.
	• Calcium antagonists are recommended if ß-blockers do not achieve sufficient symptomatic benefit or are not tolerated.
	• ACE inhibitors or nicorandil may be considered in patients with refractory symptoms.
	• Xanthine derivatives or nonpharmacological treatments such as neurostimulatory techniques may be considered in patients with symptoms refractory to the above listed drugs.
	
	<u>Stenting and peri-procedural antiplatelet strategies in stable CAD patients</u>
	• Drug-eluting stent (DES) is recommended in stable CAD patients undergoing stenting if there is no contraindication to prolonged dual antiplatelet therapy (DAPT).
	• Aspirin is recommended for elective stenting.
	• Clopidogrel is recommended for elective stenting.
	• Prasugrel or ticagrelor should be considered in patients with stent thrombosis on clopidogrel without treatment interruption.
	• GP IIb/IIIa antagonists should be considered for bailout situation only.
	• Platelet function testing or genetic testing may be considered in specific or high-risk situations (e.g., prior history of stent thrombosis; compliance issue; suspicion of resistance; high bleeding risk) if results may change the treatment strategy.
	• Prasugrel or ticagrelor may be considered in specific high-risk situations of elective stenting (e.g., left main stenting, high risk of stent thrombosis, diabetes).
	• Pretreatment with clopidogrel (when coronary anatomy is not known) is not recommended.
	• Routine platelet function testing (clopidogrel and aspirin) to adjust antiplatelet

Clinical Guideline	Recommendations
	therapy before or after elective stenting is not recommended. • Prasugrel or ticagrelor is not recommended in low-risk elective stenting. • After uncomplicated PCI, early cessation (≤1 week) of aspirin, and continuation of dual therapy with oral anticoagulation therapy and clopidogrel should be considered if the risk of stent thrombosis is low. • Triple therapy with aspirin, clopidogrel, and a DOAC for ≥1 month should be considered when the risk of stent thrombosis outweighs the bleeding risk, with a total of no more than six months. <u>Follow-up of revascularized stable coronary artery disease patients</u> • It is recommended that all revascularized patients receive a secondary prevention and be scheduled for follow-up visit. • It is recommended to instruct patients before discharge about return to work and reuptake of full activities. Patients have to be advised to seek immediate medical contact if symptoms (re-) occur. • Single antiplatelet therapy, usually aspirin, is recommended indefinitely. • DAPT is indicated after bare metal stent (BMS) for at least one month. • DAPT is indicated for six to 12 months after second generation DES. • DAPT may be used for more than one year in patients at high ischemic risk (e.g., stent thrombosis, recurrent acute coronary syndrome on DAPT, post MI/diffuse CAD) and low bleeding risk. • DAPT for one to three months may be used after DES implantation in patients at high bleeding risk or with undeferrable surgery or concomitant anticoagulant treatment. <u>Antithrombotic therapy in patients with chronic coronary syndrome:</u> • Addition of a second antithrombotic drug to aspirin for long-term secondary prevention should be considered in patients with at least a moderately increased risk of ischemic events and without high bleeding risk. • When oral anticoagulation is initiated in patients with AF, a DOAC is recommended in preference to VKA therapy.
American College of Physicians/ American College of Cardiology Foundation/ American Heart Association/ American Association for Thoracic Surgery/ Preventive Cardiovascular Nurses Association/ Society of Thoracic Surgeons: **Management of Stable Ischemic Heart Disease (2012)**[21]	<u>Medical therapy to prevent MI and death in patients with stable IHD</u> • Aspirin 75 to 162 mg daily should be continued indefinitely in the absence of contraindications. • Treatment with clopidogrel is a reasonable option when aspirin in contraindicated. • Dipyridamole should not be used as antiplatelet therapy. • Beta-blocker therapy should be initiated and continued for three years in all patients with normal left ventricular (LV) function following MI or acute coronary syndromes. • Metoprolol succinate, carvedilol, or bisoprolol should be used for all patients with systolic LV dysfunction (ejection fraction ≤40%) with heart failure or prior MI, unless contraindicated. • ACE inhibitors should be prescribed in all patients with stable IHD who also have hypertension, diabetes, LV systolic dysfunction (ejection fraction ≤40%), and/or chronic kidney disease, unless contraindicated. • Angiotensin-receptor blockers (ARBs) are recommended for patients with stable IHD who have hypertension, diabetes, LV systolic dysfunction, or chronic kidney disease and have indications for, but are intolerant of, ACE inhibitors. • Patients should receive an annual influenza vaccine. <u>Medical therapy for relief of symptoms in patients with stable IHD</u> • Beta-blockers are recommended as initial therapy for relief of symptoms. • Calcium channel blockers or long-acting nitrates should be prescribed for relief of symptoms when β-blockers are contraindicated or cause unacceptable side

Clinical Guideline	Recommendations
	effects. • Calcium channel blockers or long-acting nitrates, in combination with β-blockers, should be prescribed for relief of symptoms when initial treatment with β-blockers is unsuccessful. • Nitroglycerin or nitroglycerin spray should be used for immediate relief of angina. • Ranolazine is a fourth-line agent reserved for patients who have contraindications to, do not respond to, or cannot tolerate β-blockers, calcium-channel blockers, or long-acting nitrates.
American College of Cardiology Foundation/American Heart Association: **2014 American Heart Association/ American College of Cardiology Foundation Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes (2014)[22]**	<u>Early hospital care- standard medical therapies</u> • Supplemental oxygen should be administered to patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) with arterial oxygen saturation <90%, respiratory distress, or other high risk features of hypoxemia. • Anti-ischemic and analgesic medications o Nitrates ▪ Patients with NSTE-ACS with continuing ischemic pain should receive sublingual nitroglycerin (0.3 to 0.4 mg) every 5 minutes for up to three doses, after which an assessment should be made about the need for intravenous nitroglycerin. ▪ Intravenous nitroglycerin is indicated for patients with NSTE-ACS for the treatment of persistent ischemia, heart failure, or hypertension. ▪ Nitrates should not be administered to patients who recently received a phosphodiesterase inhibitor, especially within 24 hours of sildenafil or vardenafil, or within 48 hours of tadalafil. o Analgesic therapy ▪ In the absence of contraindications, it may be reasonable to administer morphine sulphate intravenously to patients with NSTE-ACE if there is continued ischemic chest pain despite treatment with maximally tolerated anti-ischemic medications. ▪ Nonsteroidal anti-inflammatory drugs (NSAIDs) (except aspirin) should not be initiated and should be discontinued during hospitalization due to the increased risk of major adverse cardiac event associated with their use o Beta-adrenergic blockers ▪ Oral β-blocker therapy should be initiated within the first 24 hours in patients who do not have any of the following: 1) signs of HF, 2) evidence of low-output state, 3) increased risk for cardiogenic shock, or 4) other contraindications to β-blockade (e.g., PR interval >0.24 second, second- or third-degree heart block without a cardiac pacemaker, active asthma, or reactive airway disease) ▪ In patients with concomitant NSTE-ACS, stabilized heart failure, and reduced systolic function, it is recommended to continue β-blocker therapy with one of the three drugs proven to reduce mortality in patients with heart failure: sustained-release metoprolol succinate, carvedilol, or bisoprolol. ▪ Patients with documented contraindications to β-blockers in the first 24 hours should be re-evaluated to determine subsequent eligibility. o Calcium channel blockers (CCBs) ▪ In patients with NSTE-ACS, continuing or frequently recurring ischemia, and a contraindication to β-blockers, a nondihydropyridine CCB (e.g., verapamil or diltiazem) should be given as initial therapy in the absence of clinically significant LV dysfunction, increased risk for cardiogenic shock, PR interval >0.24 seconds, or second or third degree atrioventricular block without a cardiac pacemaker. ▪ Oral nondihydropyridine calcium antagonists are recommended in patients with NSTE-ACS who have recurrent ischemia in the absence

Clinical Guideline	Recommendations
	of contraindications, after appropriate use of β-blockers and nitrates. ▪ CCBs are recommended for ischemic symptoms when β-blockers are not successful, are contraindicated, or cause unacceptable side effects. ▪ Long-acting CCBs and nitrates are recommended in patients with coronary artery spasm. ▪ Immediate-release nifedipine should not be administered to patients with NSTE-ACS in the absence of β-blocker therapy. o Other anti-ischemic interventions ▪ Ranolazine is currently indicated for treatment of chronic angina; however, it may also improve outcomes in NSTE-ACS patients due to a reduction in recurrent ischemia. o Cholesterol management ▪ High-intensity statin therapy should be initiated or continued in all patients with NSTE-ACS and no contraindications to its use. Treatment with statins reduces the rate of recurrent MI, coronary heart disease mortality, need for myocardial revascularization, and stroke. ▪ It is reasonable to obtain a fasting lipid profile in patients with NSTE-ACS, preferably within 24 hours of presentation. • Inhibitors of renin-angiotensin-aldosterone system o ACE inhibitors should be started and continued indefinitely in all patients with LVEF <0.40 and in those with hypertension, diabetes mellitus, or stable CKD, unless contraindicated. o ARBs are recommended in patients with heart failure or myocardial infarction with LVEF <0.40 who are ACE inhibitor intolerant. o Aldosterone-blockade is recommended in patients post-MI without significant renal dysfunction (creatinine >2.5 mg/dL in men or >2.0 mg/dL in women) or hyperkalemia (K >5.0 mEq/L) who are receiving therapeutic doses of ACE inhibitor and β-blocker and have a LVEF <0.40, diabetes mellitus, or heart failure. • Initial antiplatelet/anticoagulant therapy in patients with definite or likely NSTE-ACS treated with an initial invasive or ischemia-guided strategy o Non-enteric coated, chewable aspirin (162 to 325 mg) should be given to all patients with NSTE-ACS without contraindications as soon as possible after presentation, and a maintenance dose of aspirin (81 to 162 mg/day) should be continued indefinitely. o In patients who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance, a loading dose of clopidogrel followed by a daily maintenance dose should be administered. o A $P2Y_{12}$ receptor inhibitor (clopidogrel or ticagrelor) in addition to aspirin should be administered for up to 12 months to all patients with NSTE-ACS without contraindications who are treated with an early invasive or ischemia-guided strategy. Options include: ▪ Clopidogrel: 300 or 600 mg loading dose, then 75 mg daily. ▪ Ticagrelor: 180 mg loading dose, then 90 mg twice daily. ▪ It is reasonable to use ticagrelor in preference to clopidogrel for $P2Y_{12}$ treatment in patients with NSTE-ACS who undergo an early invasive or ischemia-guided strategy. ▪ In patients with NSTE-ACS treated with an early invasive strategy and dual antiplatelet therapy (DAPT) with intermediate/high-risk features (e.g., positive troponin), a GP IIb/IIIa inhibitor may be considered as part of initial antiplatelet therapy. Preferred options are eptifibatide or tirofiban. <u>Percutaneous coronary intervention (PCI)- Antiplatelet and anticoagulant therapy</u> • Antiplatelet agents o Patients already taking daily aspirin before PCI should take 81 to 325 mg

Clinical Guideline	Recommendations
	non-enteric coated aspirin before PCI o Patients not on aspirin therapy should be given non-enteric coated aspirin 325 mg as soon as possible before PCI. o After PCI, aspirin should be continued indefinitely. o A loading dose of a $P2Y_{12}$ inhibitor should be given before the procedure in patients undergoing PCI with stenting. Options include clopidogrel 600 mg, prasugrel 60 mg, or ticagrelor 180 mg. o In patients with NSTE-ACS and high-risk features (e.g., elevated troponin) not adequately pretreated with clopidogrel or ticagrelor, it is useful to administer a GP IIb/IIIa inhibitor (abciximab, double-bolus eptifibatide, or high-dose bolus tirofiban) at the time of PCI. o In patients receiving a stent (bare metal or drug eluting) during PCI, $P2Y_{12}$ inhibitor therapy should be given for at least 12 months. Options include clopidogrel 75 mg daily, prasugrel 10 mg daily, or ticagrelor 90 mg twice daily. • Anticoagulant therapy o An anticoagulant should be administered to patients with NSTE-ACS undergoing PCI to reduce the risk of intracoronary and catheter thrombus formation. o Intravenous unfractionated heparin (UFH) is useful in patients with NSTE-ACS undergoing PCI. o Bivalirudin is useful as an anticoagulant with or without prior treatment with UFH. o An additional dose of 0.3 mg/kg intravenous enoxaparin should be administered at the time of PCI to patients with NSTE-ACS who have received fewer than two therapeutic subcutaneous doses or received the last subcutaneous enoxaparin dose eight to 12 hours before PCI. o If PCI is performed while the patient is on fondaparinux, an additional 85 IU/kg of UFH should be given intravenously immediately before PCI because of the risk of catheter thrombosis (60 IU/kg IV if a GP IIb/IIIa inhibitor used with UFH dosing based on the target-activated clotting time). o Anticoagulant therapy should be discontinued after PCI unless there is a compelling reason to continue. • Timing of CABG in relation to use of antiplatelet agents o Non-enteric coated aspirin (81 to 325 mg daily) should be administered preoperatively to patients undergoing CABG. o In patients referred for elective CABG, clopidogrel and ticagrelor should be discontinued for at least five days before surgery and prasugrel for at least seven days before surgery. o In patients referred for urgent CABG, clopidogrel and ticagrelor should be discontinued for at least 24 hours to reduce major bleeding. o In patients referred for CABG, short-acting intravenous GP IIb/IIIa inhibitors (eptifibatide or tirofiban) should be discontinued for at least 2 to 4 hours before surgery and abciximab for at least 12 hours before to limit blood loss and transfusion. <u>Late hospital care, hospital discharge, and posthospital discharge care</u> • Medications at discharge o Medications required in the hospital to control ischemia should be continued after hospital discharge in patients with NSTE-ACS who do not undergo coronary revascularization, patients with incomplete or unsuccessful revascularization, and patients with recurrent symptoms after revascularization. Titration of the doses may be required. o All patients who are post–NSTE-ACS should be given sublingual or spray nitroglycerin with verbal and written instructions for its use. o Before hospital discharge, patients with NSTE-ACS should be informed

Clinical Guideline	Recommendations
	about symptoms of worsening myocardial ischemia and MI and should be given verbal and written instructions about how and when to seek emergency care for such symptoms. o Before hospital discharge, patients who are post–NSTE-ACS and/or designated responsible caregivers should be provided with easily understood and culturally sensitive verbal and written instructions about medication type, purpose, dose, frequency, side effects, and duration of use. o For patients who are post–NSTE-ACS and have initial angina lasting more than one minute, nitroglycerin (one dose sublingual or spray) is recommended if angina does not subside within three to five minutes; call 9-1-1 immediately to access emergency medical services. o If the pattern or severity of angina changes, suggesting worsening myocardial ischemia (e.g., pain is more frequent or severe or is precipitated by less effort or occurs at rest), patients should contact their clinician without delay to assess the need for additional treatment or testing. o Before discharge, patients should be educated about modification of cardiovascular risk factors. • Late hospital and post-hospital oral antiplatelet therapy o Aspirin should be continued indefinitely. The dose should be 81 mg daily in patients treated with ticagrelor and 81 to 325 mg daily in all other patients. o In addition to aspirin, a $P2Y_{12}$ inhibitor (either clopidogrel or ticagrelor) should be continued for up to 12 months in all patients with NSTE-ACS without contraindications who are treated with an ischemia-guided strategy. o In patients receiving a stent (bare-metal stent or DES) during PCI for NSTE-ACS, P2Y12 inhibitor therapy should be given for at least 12 months. • Combined oral anticoagulant therapy and antiplatelet therapy in patients with NSTE-ACS o The duration of triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a $P2Y_{12}$ receptor inhibitor in patients with NSTE-ACS should be minimized to the extent possible to limit the risk of bleeding. o Proton pump inhibitors should be prescribed in patients with NSTE-ACS with a history of gastrointestinal bleeding who require triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a $P2Y_{12}$ receptor inhibitor.
European Society of Cardiology: **Guidelines for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation (2020)[23]**	<u>Pharmacological treatment of ischemia</u> • Sublingual or intravenous nitrates and early initiation of β-blocker treatment is recommended in patients with ongoing ischemic symptoms and without contraindications. • Continuation of chronic β-blocker therapy is recommended unless the patient is in overt heart failure. • Sublingual or intravenous nitrates are recommended to relieve angina; intravenous treatment is recommended in patients with recurrent angina, uncontrolled hypertension, or signs of heart failure. • In patients with suspected/confirmed vasospastic angina, calcium channel blockers, and nitrates should be considered and β-blockers avoided. <u>Recommendations for platelet inhibition in non-ST-elevation acute coronary syndromes</u> • Aspirin is recommended for all patients without contraindications at an initial oral loading dose of 150 to 300 mg (in aspirin-naïve patients) and a maintenance dose of 75 to 100 mg/day long-term regardless of treatment strategy. • A $P2Y_{12}$ inhibitor is recommended, in addition to aspirin, for 12 months unless there are contraindications such as excessive risks of bleeds. o Ticagrelor (180 mg loading dose, 90 mg twice daily) is recommended, in the absence of contraindication, for all patients at moderate-to-high risk of ischemic events (e.g., elevated cardiac troponins), regardless of initial treatment strategy and including those pretreated with clopidogrel (which

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	should be discontinued when ticagrelor is started). ○ Prasugrel (60 mg loading dose, 10 mg daily dose) is recommended in patients who are proceeding to PCI if no contraindication. Prasugrel should be considered in preference to ticagrelor in NSTE-ACS patients who proceed to PCI. ○ Clopidogrel (300 to 600 mg loading dose, 75 mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel or who require oral anticoagulation. • $P2Y_{12}$ inhibitor administration for a shorter duration of three to six months after DES implantation may be considered in patients deemed at high bleeding risk. • Pre-treatment with a $P2Y_{12}$ inhibitor may be considered in patients with NSTE-ACS who are not planned to undergo an early invasive strategy. • It is not recommended to administer routine pre-treatment with a $P2Y_{12}$ inhibitor in patients in whom coronary anatomy is not known. • It is not recommended to administer prasugrel in patients whom coronary anatomy is not known. • GPIIb/IIIa inhibitors during PCI should be considered for bailout situations or thrombotic complications. • Cangrelor may be considered in $P2Y_{12}$ inhibitor-naïve patients undergoing PCI. • It is not recommended to administer GPIIb/IIIa inhibitors in patients whom coronary anatomy is not known. • $P2Y_{12}$ inhibitor administration in addition to aspirin beyond one year may be considered after careful assessment of the ischemic and bleeding risks of the patient. <u>Recommendations for anticoagulation in non-ST-elevation acute coronary syndromes</u> • Parenteral anticoagulation is recommended at the time of diagnosis according to both ischemic and bleeding risks. • Fondaparinux is recommended as having the most favorable efficacy-safety profile regardless of the management strategy. • Bivalirudin is recommended as an alternative to UFH plus GPIIb/IIIa inhibitors during PCI. • UFH is recommended in patients undergoing PCI who did not receive any anticoagulant. • In patients on fondaparinux undergoing PCI, a single intravenous bolus of UFH is recommended during the procedure. • Enoxaparin or UFH are recommended when fondaparinux is not available. • Enoxaparin should be considered as an anticoagulant for PCI in patients pretreated for PCI with subcutaneous enoxaparin. • Additional activated clotting time-guided intravenous boluses of UFH during PCI may be considered following initial UFH treatment. • Discontinuation of anticoagulation should be considered after PCI, unless otherwise indicated. • Crossover between UFH and LMWH is not recommended. • In NSTEMI patients with no prior stroke/TIA and at high ischemic risk as well as low bleeding risk receiving aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily for approximately one year) may be considered after discontinuation of parenteral anticoagulation. <u>Recommendations for combining antiplatelet agents and anticoagulants in non-ST-elevation acute coronary syndrome patients requiring chronic oral anticoagulation</u> • In patients with a firm indication for oral anticoagulation (e.g., atrial fibrillation with a $CHADS_2$-VASc score ≥2, recent VTE, mechanical valve prosthesis), oral anticoagulation is recommended in addition to antiplatelet therapy. • An early invasive coronary angiography (within 24 hours) should be considered

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	in moderate- to high-risk patients, irrespective of oral anticoagulant exposure, to expedite treatment allocation (medical vs PCI vs CABG) and to determine optimal antithrombotic regimen. • Initial dual antiplatelet therapy with aspirin plus a $P2Y_{12}$ inhibitor in addition to oral anticoagulation before coronary angiography is not recommended. • During PCI, additional parenteral anticoagulation is recommended, irrespective of the timing of the last dose of all non-vitamin K antagonist oral anticoagulants (NOACs) and if INR is <2.5 in VKA-treated patients. • Uninterrupted therapeutic anticoagulation with VKA or NOACs should be considered during the periprocedural phase. • Periprocedural DAPT administration consisting of aspirin and clopidogrel up to one week is recommended • Discontinuation of antiplatelet treatment in patients treated with an oral anticoagulant is recommended after 12 months • Following coronary stenting, dual (oral) antiplatelet therapy (DAPT) including new $P2Y_{12}$ inhibitors should be considered as an alternative to triple therapy for patients with non-ST-elevation acute coronary syndromes and atrial fibrillation with a $CHADS_2$-VASc score of 1 (in males) or 2 (in females). • If at low bleeding risk (HAS-BLED ≤2), triple therapy with oral anticoagulant, aspirin, and clopidogrel should be considered for six months, followed by oral anticoagulant and aspirin or clopidogrel continued up to 12 months. • If at high bleeding risk (HAS-BLED ≥3), triple therapy with oral anticoagulant, aspirin, and clopidogrel should be considered for one month, followed by oral anticoagulant and aspirin or clopidogrel continued up to 12 months irrespective of the stent type. • Dual therapy with oral anticoagulant and clopidogrel may be considered as an alternative to triple antithrombotic therapy in selected patients (HAS-BLED ≥3 and low risk of stent thrombosis). • The use of ticagrelor or prasugrel as part of triple therapy is not recommended. • In medically managed patients, one antiplatelet agent in addition to oral anticoagulant should be considered for up to one year. <u>Recommendations for post-interventional and maintenance treatment</u> • In patients with NSTE-ACS with coronary stent implantation, DAPT with a $P2Y_{12}$ inhibitor on top of aspirin is recommended for 12 months unless there are contraindications such as excessive risk of bleeding. • Adding a second anti-thrombotic agent to aspirin for extended long-term secondary prevention should be considered in patients with a moderate to high risk of ischemic events and without increased risk of major bleeding. • After stent implantation with high risk of bleeding, discontinuation of $P2Y_{12}$ inhibitor therapy after three months should be considered • After stent implantation in patients undergoing DAPT, stopping aspirin after three to six months should be considered, depending on balance between ischemic and bleeding risk. • De-escalation of $P2Y_{12}$ inhibitor treatment may be considered as an alternative DAPT strategy, especially for ACS patients deemed unsuitable for potent platelet inhibition.
American College of Cardiology/American Heart Association: **Guideline for the Management of ST-Elevation Myocardial Infarction (2013)**[24]	<u>Routine medical therapies: β-blockers</u> • Oral β-blockers should be initiated within the first 24 hours in patients with an ST-segment elevation myocardial infarction (STEMI) who do not have any of the following: 1) signs of heart failure, 2) evidence of a low-output state, 3) increased risk of cardiogenic shock, 4) other contraindications to use of oral β-blockers (e.g., PR interval >24 seconds, second or third degree heart block, active asthma, reactive airway disease). • β-blockers should be continued during and after hospitalization for all patients

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	with STEMI and with no contraindications to their use. • Patients with initial contraindications to the use of β-blockers in the first 24 hours after STEMI should be re-evaluated to determine their subsequent eligibility. • It is reasonable to administer intravenous β-blockers at the time of presentation to patients with STEMI and no contraindications to their use who are hypertensive or have ongoing ischemia. <u>Routine medical therapies: renin-angiotensin-aldosterone system inhibitors</u> • An ACE inhibitor should be administered within the first 24 hours to all patients with ST-segment elevation myocardial infarction with anterior location, heart failure, or ejection fraction ≤40%, unless contraindicated. • An ARB should be given to patients who have indications for but are intolerant of ACE inhibitors. • ACE inhibitors are reasonable for all patients with no contraindications to their use. • An aldosterone antagonist should be given to patients with STEMI and no contraindications who are already receiving an ACE inhibitor and β-blocker and who have an EF ≤40% and either symptomatic heart failure or diabetes. <u>Routine medical therapies: Lipid management</u> • High-intensity statin therapy should be initiated or continued in all patients with STEMI and no contraindications to its use. • It is reasonable to obtain a fasting lipid profile in patients with STEMI, preferably within 24 hours of presentation.
European Society of Cardiology: **Management of Acute Myocardial Infarction in Patients Presenting with ST-segment Elevation (2017)**[25]	<u>Routine therapies in the acute, subacute and long term phase of ST-elevation myocardial infarction (STEMI)</u> • Antiplatelet therapy with low dose aspirin (75 to 100 mg) is indicated indefinitely after STEMI. • Dual antiplatelet therapy with a combination of aspirin and prasugrel or aspirin and ticagrelor is recommended for 12 months after percutaneous coronary intervention (PCI), unless there are contraindications such as excessive risk of bleeding. • A proton pump inhibitor (PPI) in combination with dual antiplatelet therapy is recommended in patients at high risk of gastrointestinal bleeding. • In patients with an indication for oral anticoagulation, oral anticoagulants are indicated in addition to antiplatelet therapy. • In patients who are at high risk of severe bleeding complications, discontinuation of $P2Y_{12}$ inhibitor therapy after six months should be considered. • In STEMI patients with stent implantation and an indication for oral anticoagulation, triple therapy (oral anticoagulant, aspirin, and clopidogrel) should be considered for one to six months (according a balance between the estimated risk of recurrent coronary events and bleeding). • In patients with left ventricular thrombus, anticoagulation should be instituted for a minimum of six months, guided by repeated imaging. • In selected patients who receive aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily) may be considered if the patient is at low bleeding risk. • Dual antiplatelet therapy should be used up to one year in patients with STEMI who did not receive a stent unless there are contraindications such as excessive risk of bleeding. • In high ischemic-risk patients (age ≥50 years, and at least one of the following risk factors: age ≥65 years, diabetes mellitus on medication, prior spontaneous MAI, multivessel CAD, or chronic renal dysfunction with eGFR <60 mL/min) who have tolerated dual antiplatelet therapy without a bleeding complication, treatment with dual antiplatelet therapy in the form of ticagrelor 60 mg twice a day on top of aspirin for longer than 12 months may be considered for up to three

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	years. • The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with aspirin and oral anticoagulation. • Oral treatment with β-blockers should be considered during hospital stay and continued thereafter in all patients without contraindications. • Oral treatment with β-blockers is indicated in patients with heart failure or left ventricular dysfunction, LVEF ≤40% unless contraindicated. • Intravenous β-blockers must be avoided in patients with hypotension or acute heart failure or AV block or severe bradycardia. • Intravenous β-blockers should be considered at the time of presentation in patients undergoing primary PCI without contraindications, with high blood pressure, tachycardia, and no signs of heart failure. • A fasting lipid profile must be obtained in all STEMI patients, as soon as possible after presentation. • It is recommended to initiate or continue high dose statins early after admission in all STEMI patients without contraindication or history of intolerance, regardless of initial cholesterol values and maintain it long-term. • An LDL-C goal of <1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline LDL-C is between 1.8 to 3.5 mmol/L (70 to 135 mg/dL) is recommended. • In patients with LDL-C >1.8 mmol/L (>70 mg/dL) despite a maximally tolerated statin dose who remain at high risk, further therapy to reduce LDL-C should be considered. • ACE inhibitors are indicated starting within the first 24 hours of STEMI in patients with evidence of heart failure, LV systolic dysfunction, diabetes or an anterior infarct. • An ARB, preferably valsartan, is an alternative to ACE inhibitors in patients with heart failure or LV systolic dysfunction, particularly those who are intolerant to ACE inhibitors. • ACE inhibitors should be considered in all patients in the absence of contraindications. • Aldosterone antagonists, e.g. eplerenone, are indicated in patients with an ejection fraction ≤40% and heart failure or diabetes, provided no renal failure or hyperkalemia.
American College of Cardiology/ American Heart Association: **Guideline on the Primary Prevention of Cardiovascular Disease (2019)[26]**	Top 10 messages for the primary prevention of cardiovascular disease • The most important way to prevent atherosclerotic vascular disease, heart failure, and atrial fibrillation is to promote a healthy lifestyle throughout life. • A team-based care approach is an effective strategy for the prevention of cardiovascular disease. Clinicians should evaluate the social determinants of health that affect individuals to inform treatment decisions. • Adults who are 40 to 75 years of age and are being evaluated for cardiovascular disease prevention should undergo 10-year atherosclerotic cardiovascular disease (ASCVD) risk estimation and have a clinician–patient risk discussion before starting on pharmacological therapy, such as antihypertensive therapy, a statin, or aspirin. In addition, assessing for other risk-enhancing factors can help guide decisions about preventive interventions in select individuals, as can coronary artery calcium scanning. • All adults should consume a healthy diet that emphasizes the intake of vegetables, fruits, nuts, whole grains, lean vegetable or animal protein, and fish and minimizes the intake of trans fats, processed meats, refined carbohydrates, and sweetened beverages. For adults with overweight and obesity, counseling and caloric restriction are recommended for achieving and maintaining weight loss. • Adults should engage in at least 150 minutes per week of accumulated moderate-intensity physical activity or 75 minutes per week of vigorous-intensity physical

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	activity. • For adults with type 2 diabetes mellitus, lifestyle changes, such as improving dietary habits and achieving exercise recommendations, are crucial. If medication is indicated, metformin is first-line therapy, followed by consideration of a sodium-glucose cotransporter 2 inhibitor or a glucagon-like peptide-1 receptor agonist. • All adults should be assessed at every healthcare visit for tobacco use, and those who use tobacco should be assisted and strongly advised to quit. • Aspirin should be used infrequently in the routine primary prevention of ASCVD because of lack of net benefit. • Statin therapy is first-line treatment for primary prevention of ASCVD in patients with elevated low-density lipoprotein cholesterol levels (≥190 mg/dL), those with diabetes mellitus, who are 40 to 75 years of age, and those determined to be at sufficient ASCVD risk after a clinician–patient risk discussion. • Nonpharmacological interventions are recommended for all adults with elevated blood pressure or hypertension. For those requiring pharmacological therapy, the target blood pressure should generally be <130/80 mm Hg. <u>Adults with Type 2 Diabetes Mellitus</u> • For all adults with T2DM, a tailored nutrition plan focusing on a heart-healthy dietary pattern is recommended to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors. • Adults with T2DM should perform at least 150 minutes per week of moderate-intensity physical activity or 75 minutes of vigorous-intensity physical activity to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors. • For adults with T2DM, it is reasonable to initiate metformin as first-line therapy along with lifestyle therapies at the time of diagnosis to improve glycemic control and reduce ASCVD risk. • For adults with T2DM and additional ASCVD risk factors who require glucose-lowering therapy despite initial lifestyle modifications and metformin, it may be reasonable to initiate a sodium-glucose cotransporter 2 (SGLT-2) inhibitor or a glucagon-like peptide-1 receptor (GLP-1R) agonist to improve glycemic control and reduce CVD risk. <u>Adults with high blood cholesterol</u> • In adults at intermediate risk (≥7.5% to <20% 10-year ASCVD risk), statin therapy reduces risk of ASCVD, and in the context of a risk discussion, if a decision is made for statin therapy, a moderate-intensity statin should be recommended. • In intermediate risk (≥7.5% to <20% 10-year ASCVD risk) patients, LDL-C levels should be reduced by 30% or more, and for optimal ASCVD risk reduction, especially in patients at high risk (≥20% 10-year ASCVD risk), levels should be reduced by 50% or more. • In adults 40 to 75 years of age with diabetes, regardless of estimated 10-year ASCVD risk, moderate-intensity statin therapy is indicated. • In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL (≥4.9 mmol/L) or higher, maximally tolerated statin therapy is recommended. • In adults with diabetes mellitus who have multiple ASCVD risk factors, it is reasonable to prescribe high-intensity statin therapy with the aim to reduce LDL-C levels by 50% or more. • In intermediate-risk (≥7.5% to <20% 10-year ASCVD risk) adults, risk-enhancing factors favor initiation or intensification of statin therapy. • In intermediate-risk (≥7.5% to <20% 10-year ASCVD risk) adults or selected borderline-risk (5% to <7.5% 10-year ASCVD risk) adults in whom a coronary

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	artery calcium score is measured for the purpose of making a treatment decision, AND o If the coronary artery calcium score is zero, it is reasonable to withhold statin therapy and reassess in five to 10 years, as long as higher-risk conditions are absent (e.g., diabetes, family history of premature CHD, cigarette smoking); o If coronary artery calcium score is one to 99, it is reasonable to initiate statin therapy for patients ≥55 years of age; o If coronary artery calcium score is 100 or higher or in the 75th percentile or higher, it is reasonable to initiate statin therapy. • In patients at borderline risk (5% to <7.5% 10-year ASCVD risk), in risk discussion, the presence of risk-enhancing factors may justify initiation of moderate-intensity statin therapy. <u>Adults with high blood pressure or hypertension</u> • In adults with elevated blood pressure (BP) or hypertension, including those requiring antihypertensive medications nonpharmacological interventions are recommended to reduce BP. These include: o weight loss; o a heart-healthy dietary pattern; o sodium reduction; o dietary potassium supplementation; o increased physical activity with a structured exercise program; and o limited alcohol. • In adults with an estimated 10-year ASCVD risk (ACC/AHA pooled cohort equations to estimate 10-year risk of ASCVD) of 10% or higher and an average systolic BP (SBP) of 130 mm Hg or higher or an average diastolic BP (DBP) of 80 mm Hg or higher, use of BP-lowering medications is recommended for primary prevention of CVD. • In adults with confirmed hypertension and a 10-year ASCVD event risk of 10% or higher, a BP target of less than 130/80 mm Hg is recommended. • In adults with hypertension and chronic kidney disease, treatment to a BP goal of less than 130/80 mm Hg is recommended. • In adults with T2DM and hypertension, antihypertensive drug treatment should be initiated at a BP of 130/80 mm Hg or higher, with a treatment goal of less than 130/80 mm Hg. • In adults with an estimated 10-year ASCVD risk <10% and an SBP of 140 mm Hg or higher or a DBP of 90 mm Hg or higher, initiation and use of BP-lowering medication are recommended. • In adults with confirmed hypertension without additional markers of increased ASCVD risk, a BP target of less than 130/80 mm Hg may be reasonable. <u>Recommendations for treatment of tobacco use</u> • All adults should be assessed at every healthcare visit for tobacco use and their tobacco use status recorded as a vital sign to facilitate tobacco cessation. • To achieve tobacco abstinence, all adults who use tobacco should be firmly advised to quit. • In adults who use tobacco, a combination of behavioral interventions plus pharmacotherapy is recommended to maximize quit rates. • In adults who use tobacco, tobacco abstinence is recommended to reduce ASCVD risk. • To facilitate tobacco cessation, it is reasonable to dedicate trained staff to tobacco treatment in every healthcare system. • All adults and adolescents should avoid secondhand smoke exposure to reduce ASCVD risk.

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	Recommendations for aspirin use • Low-dose aspirin (75 to 100 mg orally daily) might be considered for the primary prevention of ASCVD among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk. • Low-dose aspirin (75 to 100 mg orally daily) should not be administered on a routine basis for the primary prevention of ASCVD among adults >70 years of age. • Low-dose aspirin (75 to 100 mg orally daily) should not be administered for the primary prevention of ASCVD among adults of any age who are at increased risk of bleeding.
American Heart Association/American College of Cardiology/ Heart Failure Society of America: **2022 AHA/ACC /HFSA Guideline for the Management of Heart Failure (2022)**[27]	Treatment of Stage A heart failure (HF) • Hypertension should be controlled in accordance with guideline-directed medication therapy for hypertension to prevent symptomatic HF. (LoE: A) • In patients with type 2 diabetes and either established CVD or at high cardiovascular risk, SGLT-2 inhibitors should be used to prevent hospitalizations for HF. (LoE: A) • In the general population, healthy lifestyle habits such as regular physical activity, maintaining normal weight, healthy dietary patterns, and avoiding smoking are helpful to reduce future risk of HF. (LoE: B) • Patients at risk of developing HF, natriuretic peptide biomarker-based screening followed by team-based care, including a cardiovascular specialist optimizing therapy, can be useful to prevent the development of LV dysfunction (systolic or diastolic) or new-onset HF. (LoE: B) Treatment of Stage B heart failure • In patients with LVEF≤40%, ACE inhibitors should be used to prevent HF and reduce mortality. (LoE: A) • In patients with a recent or remote history of MI or ACS, statins should be used to prevent symptomatic HF and adverse cardiovascular events. (LoE: A) • In patients with a recent MI and LVEF≤40% who are intolerant to ACE inhibitors, ARB should be used to prevent symptomatic HF and reduce mortality. (LoE: B) • In patients with a recent or remote history of MI or ACS and LVEF≤40%, evidence-based beta blockers should be used to reduce mortality. (LoE: B) • In patients who are at least 40 days post-MI with LVEF ≤30% and NYHA class I symptoms while receiving guideline-directed medication therapy and have reasonable expectation of meaningful survival for greater than one year, an implantable cardioverter-defibrillator is recommended for primary prevention of sudden cardiac death to reduce total mortality. (LoE: B) • In patients with LVEF ≤40%, beta blockers should be used to prevent symptomatic HF. (LoE: C) • In patients with LVEF ≤50%, thiazolidinediones should not be used because they increase the risk of HF, including hospitalizations. (LoE: B) • In patients with LVEF ≤50%, nondihydropyridine calcium channel blockers with negative inotropic effects may be harmful. (LoE: C) Treatment for Stage C Heart Failure with Reduced Ejection Fraction (HFrEF) • For patients with stage C HF, avoiding excessive sodium intake is reasonable to reduce congestive symptoms. (LoE: C) • In patients with HF who have fluid retention, diuretics are recommended to relieve congestion, improve symptoms, and prevent worsening HF. (LoE: B) • For patients with HF and congestive symptoms, addition of a thiazide (e.g., metolazone) to treatment with a loop diuretic should be reserved for patients who

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	do not respond to moderate or high dose loop diuretics to minimize electrolyte abnormalities. (LoE: B) • In patients with HFrEF and NYHA class II to III symptoms, the use of an ARNI is recommended to reduce morbidity and mortality. (LoE: A) • In patients with previous or current symptoms of chronic HFrEF, the use of an ACE inhibitor is beneficial to reduce morbidity and mortality when the use of an ARNI is not feasible. (LoE: A) • In patients with previous or current symptoms of chronic HFrEF, who are intolerant to an ACE inhibitor because of cough or angioedema, and when the use of an ARNI is not feasible, the use of an ARB is recommended to reduce morbidity and mortality. (LoE: A) • In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality. (LoE: B) • ARNIs should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor. (LoE: B) • ARNI or ACE inhibitors should not be administered in patients with a history of angioedema. (LoE: C) • In patients with HFrEF, with current or previous symptoms, use of one of the three β-blockers proven to reduce mortality (e.g., bisoprolol, carvedilol, sustained-release metoprolol succinate) is recommended to reduce mortality and hospitalizations. (LoE: A) • In patients with HFrEF and NYHA class II to IV symptoms, a mineralocorticoid receptor antagonist (spironolactone or eplerenone) is recommended to reduce morbidity and mortality, if eGFR is >30 mL/min/1.73 m^2 and serum potassium is <5.0 mEq/L. Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely followed thereafter to minimize risk of hyperkalemia and renal insufficiency. (LoE: A) • In patients taking a mineralocorticoid receptor antagonist whose serum potassium cannot be maintained at <5.5 mEq/L, mineralocorticoid receptor antagonist should be discontinued to avoid life threatening hyperkalemia. (LoE: B) • In patients with symptomatic chronic HFrEF, SGLT-2 an inhibitor is recommended to reduce hospitalization for HF and cardiovascular mortality, irrespective of the presence of type 2 diabetes. (LoE: A) • The combination of hydralazine and isosorbide dinitrate is recommended to improve symptoms and reduce morbidity and mortality for patients self-identified as African Americans with NYHA class III to IV HFrEF receiving optimal therapy. (LoE: A) • In patients with current or previous symptomatic HFrEF who cannot be given first-line agents, such as an ARNI, ACE inhibitor or ARB because of drug intolerance or renal insufficiency, a combination of hydralazine and isosorbide dinitrate might be considered to reduce morbidity and mortality. (LoE: C) • In patients with HF class II to IV symptoms, omega-3 polyunsaturated fatty acid supplementation may be reasonable to use as adjunctive therapy to reduce mortality and cardiovascular hospitalizations. (LoE: B) • In patients with chronic HFrEF without specific indication (e.g., venous thromboembolism, atrial fibrillation, a previous thromboembolic event, or a cardioembolic source, anticoagulation is not recommended. (LoE: B) • Dihydropyridine and non-dihydropyridine calcium channel blockers are not recommended for patients with HFrEF. (LoE: A) • In patients with HFrEF, vitamins, nutritional supplements, and hormonal therapy are not recommended other than to correct specific deficiencies. (LoE: B) • In patients with HFrEF, class IC antiarrhythmic medication and dronedarone may increase risk of mortality. (LoE: A) • In patients with HFrEF, thiazolidinediones increase the risk of worsening HF

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	symptoms and hospitalizations. (LoE: A) • In patients with type 2 diabetes and high cardiovascular risk, the DPP-4 inhibitors, saxagliptin and alogliptin, increase the risk of HF hospitalization and should be avoided in patients with HF. (LoE: B) • In patients with HFrEF, nonsteroidal anti-inflammatory drugs worsen HF symptoms and should be avoided or withdrawn whenever possible. (LoE: B) • For patients with symptomatic (NYHA class II to III) stable chronic HFrEF (LVEF ≤35%) who are receiving guideline-directed medical therapy, including a maximally tolerated dose of a beta blocker, and who are in sinus rhythm with a heart rate of ≥70 beats per minute at rest, ivabradine can be beneficial to reduce HF hospitalizations and cardiovascular death. (LoE: B) • In patients with symptomatic HFrEF despite guideline-directed medical therapy or who are unable to tolerate guideline-directed medical therapy, digoxin might be considered to decrease hospitalizations for HF. (LoE: B) • In select high-risk patients with HFrEF and recent worsening of HF already on guideline-directed medical therapy, an oral soluble guanylate cyclase stimulator (vericiguat) may be considered to reduce HF hospitalization and cardiovascular death. (LoE: B) <u>Pharmacological treatment for Stage C HF with mildly reduced EF and improved EF</u> • In patients with HF with mildly reduced EF, SGLT-2 inhibitors can be beneficial in decreasing HF hospitalizations and cardiovascular mortality. (LoE: B) • Among patients with current or previous symptomatic HF with mildly reduced EF (LVEF, 41 to 49%), use of evidence-based beta blockers for HFrEF, ARNI, ACE inhibitor or ARB, and mineralocorticoid receptor antagonists may be considered to reduce the risk of HF hospitalization and cardiovascular mortality, particularly among patients with LVEF on the lower end of this spectrum. (LoE: B) • In patients with HF with improved EF after treatment, guideline-directed medical therapy should be continued to prevent relapse of HF and LV dysfunction, even in patients who may become asymptomatic. (LoE: B) <u>Pharmacological treatment for Stage C HF with preserved EF (HFpEF)</u> • Patients with hypertension and HFpEF should have medication titrated to attain blood pressure targets in accordance with published clinical practice guidelines to prevent morbidity. (LoE: C) • SGLT-2 inhibitors can be beneficial in decreasing HF hospitalizations and cardiovascular mortality. (LoE: B) • In patients with HFpEF, the use of a mineralocorticoid receptor antagonist, ARB, or ARNI may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum. (LoE: B) • Routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or quality of life in patients with HFpEF is ineffective. (LoE: B) <u>Treatment of Stage D (advanced/refractory) HF</u> • For patients with advanced HF and hyponatremia, the benefit of fluid restriction to reduce congestive symptoms is uncertain. (LoE: C) • Continuous intravenous inotropic support is reasonable as “bridge therapy” in patients with HF (Stage D) refractory to guideline-directed medical therapy and device therapy who are eligible for and awaiting mechanical circulatory support or cardiac transplantation. (LoE: B) • In select patients with HF Stage D, despite optimal guideline-directed medical therapy and device therapy who are ineligible for either mechanical circulatory support or cardiac transplantation, continuous intravenous inotropic support may be considered as palliative therapy for symptom control and improvement in

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	functional status. (LoE: B) • Long-term use of either continuous or intermittent, intravenous inotropic agents, for reasons other than palliative care or as a bridge to advanced therapies, is potentially harmful. (LoE: B)
European Society of Cardiology: **Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (2021)**[28]	<u>Pharmacological treatments indicated in patients with (NYHA Class II-IV) heart failure with reduced ejection fraction</u> • An ACE inhibitor is recommended, in addition to a β-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death. • A mineralocorticoid receptor antagonist (MRA) is recommended for patients with HFrEF, who remain symptomatic despite treatment with an ACE inhibitor and a β-blocker, to reduce the risk of HF hospitalization and death. • Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death. Dapagliflozin or empagliflozin are recommended, in addition to optimal medical therapy with an ACE-I/ARNI, a β-blocker and an MRA, for patients with HFrEF regardless of diabetes status. • Sacubitril-valsartan is recommended as a replacement for an ACE inhibitor to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE inhibitor, a β-blocker, and a mineralocorticoid receptor antagonist. • Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion. • Ivabradine should be considered to reduce the risk of HF hospitalization or cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm despite treatment with an evidence-based dose of β-blocker (or maximum tolerated dose below that), ACE inhibitor (or ARB), and a mineralocorticoid receptor antagonist (or ARB). • Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm who are unable to tolerate or have contraindications for a β-blocker. Patients should also receive an ACE inhibitor (or ARB) and a mineralocorticoid receptor antagonist (or ARB). • An ARB is recommended to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients unable to tolerate an ACE inhibitor (patients should also receive a β-blocker and mineralocorticoid receptor antagonist). • An ARB may be considered to reduce the risk of HF hospitalization and death in patients who are symptomatic despite treatment with a β-blocker who are unable to tolerate a mineralocorticoid receptor antagonist. • Vericiguat may be considered in patients in NYHA class II-IV who have had worsening HF despite treatment with an ACE-I (or ARNI), a β-blocker and an MRA to reduce the risk of CV mortality or HF hospitalization. • Hydralazine and isosorbide dinitrate should be considered in self-identified black patients with LVEF ≤35% or with an LVEF <45% combined with a dilated LV in NYHA Class III–IV despite treatment with an ACE-I a β-blocker and a mineralocorticoid receptor antagonist to reduce the risk of HF hospitalization and death. • Hydralazine and isosorbide dinitrate may be considered in symptomatic patients with HFrEF who can tolerate neither an ACE inhibitor nor an ARB (or they are contraindicated) to reduce the risk of death. • Digoxin is a treatment with less-certain benefits and may be considered in symptomatic patients in sinus rhythm despite treatment with an ACE inhibitor (or ARB), a β-blocker and a mineralocorticoid receptor antagonist, to reduce the risk of hospitalization (both all-cause and HF-hospitalizations). <u>Recommendations for treatment of patients with (NYHA class II-IV) heart failure</u>

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	with mildly reduced ejection fraction (HFmrEF) • Diuretics are recommended in patients with congestion and HFmrEF in order to alleviate symptoms and signs. • An ACE inhibitor may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • An ARB may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • A β-blocker may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • An MRA may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • Sacubitril/valsartan may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. Recommendations for treatment of patients with heart failure with preserved ejection fraction (HFpEF) • It is recommended to screen patients with HFpEF for both cardiovascular and noncardiovascular comorbidities, which, if present, should be treated provided safe and effective interventions exist to improve symptoms, well-being and/or prognosis. • Diuretics are recommended in congested patients with HFpEF in order to alleviate symptoms and signs. Recommendations for the primary prevention of heart failure in patients with risk factors for its development • Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life. • Treatment with statins is recommended in patients at high risk of CV disease or with CV disease in order to prevent or delay the onset of HF, and to prevent HF hospitalizations. • SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with diabetes at high risk of CV disease or with CV disease in order to prevent HF hospitalizations. • Counselling against sedentary habit, obesity, cigarette smoking, and alcohol abuse is recommended to prevent or delay the onset of HF. Recommendations for the initial management of patients with acute heart failure – pharmacotherapy • Intravenous loop diuretics are recommended for all patients with acute HF admitted with signs/symptoms of fluid overload to improve symptoms. It is recommended to regularly monitor symptoms, urine output, renal function and electrolytes during use of intravenous diuretics. • Combination of a loop diuretic with thiazide type diuretic should be considered in patients with resistant oedema who do not respond to an increase in loop diuretic doses. • In patients with acute HF and SBP >110 mmHg, intravenous vasodilators may be considered as initial therapy to improve symptoms and reduce congestion. • Inotropic agents may be considered in patients with SBP <90 mmHg and evidence of hypoperfusion who do not respond to standard treatment, including fluid challenge, to improve peripheral perfusion and maintain end-organ function. • Inotropic agents are not recommended routinely, due to safety concerns, unless the patient has symptomatic hypotension and evidence of hypoperfusion. • A vasopressor, preferably norepinephrine, may be considered in patients with cardiogenic shock to increase blood pressure and vital organ perfusion. • Thromboembolism prophylaxis (e.g., with LMWH) is recommended in patients

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	not already anticoagulated and with no contraindication to anticoagulation, to reduce the risk of deep venous thrombosis and pulmonary embolism. • Routine use of opiates is not recommended, unless in selected patients with severe/intractable pain or anxiety.
Eighth Joint National Committee (JNC 8): **2014 Evidence-based Guideline for the Management of High Blood Pressure in Adults (2014)**[29]	• Pharmacologic treatment should be initiated in patients ≥60 years of age to lower blood pressure at systolic blood pressure ≥150 mm Hg or diastolic blood pressure ≥90 mm Hg and to a goal systolic blood pressure <150 mm Hg and goal diastolic blood pressure <90 mm Hg. Adjustment of treatment is not necessary if treatment results in lower blood pressure and treatment is well tolerated and without adverse effects on health or quality of life. • In patients <60 years of age, pharmacologic treatment should be initiated to lower blood pressure at diastolic blood pressure ≥90 mm Hg to a goal diastolic blood pressure <90 mm Hg. • In patients <60 years of age, pharmacologic treatment should be initiated to lower blood pressure at systolic blood pressure ≥150 mm Hg to a goal diastolic blood pressure <140 mm Hg. • For patients ≥18 years of age with chronic kidney disease or diabetes, pharmacologic treatment should be initiated to lower blood pressure at systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg and to a goal systolic blood pressure <140 mm Hg and goal diastolic blood pressure <90 mm Hg. • Initial antihypertensive treatment for the general nonblack population, including those with diabetes, should include thiazide-type diuretic, calcium channel blocker (CCB), ACE inhibitor, or ARB. • Initial antihypertensive treatment for the general black population, including those with diabetes, should include thiazide-type diuretic or CCB. • For patients ≥18 years of age with chronic kidney disease regardless of race or diabetes status, initial (or add-on) treatment should include an ACE inhibitor or ARB to improve kidney outcomes. • The main goal of antihypertensive treatment is to attain and maintain goal blood pressure. • If goal blood pressure is not attained within a month of treatment, the dose of the initial drug should be increased or second drug from the thiazide-type diuretic, CCB, ACE inhibitor, or ARB classes should be added. • If goal is not achieved with two drugs, a third drug from the thiazide-type diuretic, CCB, ACE inhibitor, or ARB classes should be added. • An ACE inhibitor and ARB should not be used together. • Antihypertensive classes can be used if the patient is unable to achieve goal blood pressure with three agents or had a contraindication to a preferred class. • If blood pressure is not able to be achieved or in complicated patients, referral to a hypertension specialist may be indicated.
International Society of Hypertension: **Global Hypertension Practice Guidelines (2020)**[30]	<u>Lifestyle modifications</u> • Lifestyle modification is the first line of antihypertensive treatment. • Salt reduction: Reduce salt added when preparing foods, and at the table. Avoid or limit consumption of high salt foods such as soy sauce, fast foods and processed food including breads and cereals high in salt. • Healthy diet: Eating a diet that is rich in whole grains, fruits, vegetables, polyunsaturated fats and dairy products and reducing food high in sugar, saturated fat and trans fats, such as the DASH diet. • Healthy drinks: Moderate consumption of coffee, green and black tea. Other beverages that can be beneficial include karkadé (hibiscus) tea, pomegranate juice, beetroot juice and cocoa. • Moderation of alcohol consumption: The recommended daily limit for alcohol consumptions is 2 standard drinks for men and 1.5 for women (10 g alcohol/standard drink). Avoid binge drinking.

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	• Weight reduction: Body weight control is indicated to avoid obesity. Particularly abdominal obesity should be managed. Ethnic-specific cut-offs for BMI and waist circumference should be used. Alternatively, a waist-to-height ratio <0.5 is recommended for all populations. • Smoking cessation: Smoking is a major risk factor for cardiovascular disease (CVD), COPD and cancer. Smoking cessation and referral to smoking cessation programs are advised. • Regular physical activity: Studies suggest that regular aerobic and resistance exercise may be beneficial for both the prevention and treatment of hypertension. Moderate intensity aerobic exercise (walking, jogging, cycling, yoga, or swimming) for 30 minutes on five to seven days per week Strength training also can help reduce blood pressure. Performance of resistance/strength exercises on two to three days per week. • Reduce stress and induce mindfulness: Stress should be reduced and mindfulness or meditation introduced into the daily routine. • Reduce exposure to air pollution and cold temperature: Evidence from studies support a negative effect of air pollution on blood pressure in the long-term. <u>Pharmacological Treatment</u> • Ideal characteristics of drug treatment o Treatments should be evidence-based in relation to morbidity/mortality prevention. o Use a once-daily regimen which provides 24-hour blood pressure control. o Treatment should be affordable and/or cost-effective relative to other agents. o Treatments should be well-tolerated. o Evidence of benefits of use of the medication in populations to which it is to be applied. • General scheme for drug treatment o Lifestyle modification is the first line of antihypertensive treatment. o Grade 1 hypertension (BP 140 to 159/ 90 to 99): Immediate drug treatment in high-risk patients or those with CVD, chronic kidney disease (CKD), diabetes mellitus (DM), or hypertension-mediated organ damage (HMOD). Drug treatment after three to six months of lifestyle intervention if BP still not controlled in low to moderate risk patients. o Grade 2 hypertension (BP ≥160/100): Immediate drug treatment in all patients. • Core drug-treatment strategy o Step 1: Dual low-dose combination (ACE inhibitor or ARB plus dihydropyridine-calcium channel blockers (DHP-CCB)); consider monotherapy in low-risk grade 1 hypertension or in very old (≥80 years) or frail patients; consider ACE/ARB plus thiazide-like diuretic in post-stroke, very elderly, incipient HF, or CCB intolerance; consider ACE/ARB plus DHP-CCB or DHP-CCB plus thiazide-like diuretics in black patients. o Step 2: Dual full-dose combination (ACE inhibitor or ARB plus DHP-CCB); consider monotherapy in low-risk grade 1 hypertension or in very old (≥80 years) or frail patients; consider ACE/ARB plus thiazide-like diuretic in post-stroke, very elderly, incipient HF, or CCB intolerance. o Step 3: Triple combination (ACE/ARB plus DHP-CCB plus thiazide-like diuretic). o Step 4, resistant hypertension: triple combination plus spironolactone or other drug, alternatives include amiloride, doxazosin, eplerenone, clonidine, or β-blocker. Caution with spironolactone or other potassium sparing diuretics when estimated GFR <45 mL/min/1.73m^2 or K+ >4.5

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	mmol/L. ○ Consider β-blockers at any treatment step when there is a specific indication for their use, e.g., heart failure, angina, post-MI, atrial fibrillation, or younger women planning pregnancy or pregnant.
Hypertension Canada: **2020 Guidelines for the Prevention, Diagnosis, Risk Assessment, and Treatment of Hypertension in Adults and Children (2020)**[31]	Indications for drug therapy for adults with hypertension without compelling indications for specific agents • Antihypertensive therapy should be prescribed for average diastolic blood pressure (DBP) measurements of ≥100 mmHg or average systolic blood pressure (SBP) measurements of ≥160 mmHg in patients without macrovascular target organ damage or other cardiovascular risk factors. • Antihypertensive therapy should be strongly considered for average DPB readings ≥90 mmHg or for average SBP readings ≥140 mmHg in the presence of macrovascular target organ damage or other independent cardiovascular risk factors. • For high-risk patients, aged 50 years or older, with SBP levels ≥130 mmHg, intensive management to target a SBP <120 mmHg should be considered. Patient selection for intensive management is recommended and caution should be taken in certain high-risk groups. Indications for drug therapy for adults with diastolic and with or without systolic hypertension • Initial therapy should be with either monotherapy or single pill combination (SPC). ○ Recommended monotherapy choices are: ▪ A thiazide/thiazide-like diuretic, with longer-acting diuretics preferred; ▪ A β-blocker (in patients <60 years of age); ▪ An angiotensin-converting enzyme (ACE) inhibitor (in nonblack patients); ▪ An angiotensin receptor blocker (ARB); or ▪ A long-acting calcium channel blocker (CCB). ○ Recommended SPC choices are those in which an ACE inhibitor is combined with a CCB, ARB with a CCB, or ACE inhibitor or ARB with a diuretic. ○ Hypokalemia should be avoided in patients treated with thiazide/thiazide-like diuretic monotherapy. • Additional antihypertensive drugs should be used if target BP levels are not achieved with standard-dose monotherapy. Add-on drugs should be chosen from first-line choices. Useful choices include a thiazide/thiazide-like diuretic or CCB with either: ACE inhibitor, ARB, or β-blocker. Caution should be exercised in combining a nondihydropyridine CCB and a β-blocker. The combination of an ACE inhibitor and an ARB is not recommended. • If BP is still not controlled with a combination of two or more first-line agents, or there are adverse effects, other antihypertensive drugs may be added. • Possible reasons for poor response to therapy should be considered. • α-Blockers are not recommended as first-line agents for uncomplicated hypertension; β-blockers are not recommended as first-line therapy for uncomplicated hypertension in patients ≥60 years of age; and ACE inhibitors are not recommended as first-line therapy for uncomplicated hypertension in black patients. However, these agents may be used in patients with certain comorbid conditions or in combination therapy. Indications for drug therapy for adults with isolated systolic hypertension • Initial therapy should be single-agent therapy with a thiazide/thiazide-like diuretic, a long-acting dihydropyridine CCB, or an ARB. If there are adverse effects, another drug from this group should be substituted. Hypokalemia should

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	be avoided in patients treated with thiazide/thiazide-like diuretic monotherapy. • Additional antihypertensive drugs should be used if target BP levels are not achieved with standard-dose monotherapy. Add-on drugs should be chosen from first-line options. • If BP is still not controlled with a combination of two or more first-line agents, or there are adverse effects, other classes of drugs (such as α-blockers, ACE inhibitors, centrally acting agents, or nondihydropyridine CCBs) may be combined or substituted. • Possible reasons for poor response to therapy should be considered. • α-Blockers are not recommended as first-line agents for uncomplicated isolated systolic hypertension; and β-blockers are not recommended as first-line therapy for isolated systolic hypertension in patients ≥60 years of age. However, both agents may be used in patients with certain comorbid conditions or in combination therapy. <u>Guidelines for hypertensive patients with coronary artery disease (CAD)</u> • For most hypertensive patients with CAD, an ACE inhibitor or ARB is recommended. • For hypertensive patients with CAD, but without coexisting systolic heart failure, the combination of an ACE inhibitor and ARB is not recommended. • For high-risk hypertensive patients, when combination therapy is being used, choices should be individualized. The combination of an ACE inhibitor and a dihydropyridine CCB is preferable to an ACE inhibitor and a thiazide/thiazide-like diuretic in selected patients. • For patients with stable angina pectoris but without previous heart failure, myocardial infarction, or coronary artery bypass surgery, either a β-blocker or CCB can be used as initial therapy. • Short-acting nifedipine should not be used. • When decreasing SBP to target levels in patients with established CAD (especially if isolated systolic hypertension is present), be cautious when the DBP is ≤60 mmHg because of concerns that myocardial ischemia might be exacerbated, especially in patients with left ventricular hypertrophy (LVH). <u>Guidelines for patients with hypertension who have had a recent myocardial infarction</u> • Initial therapy should include a β-blocker as well as an ACE inhibitor. • An ARB can be used if the patient is intolerant of an ACE inhibitor. • CCBs may be used in patients after myocardial infarction when β-blockers are contraindicated or not effective. Nondihydropyridine CCBs should not be used when there is heart failure, evidenced by pulmonary congestion on examination or radiography. <u>Treatment of hypertension in association with heart failure</u> • In patients with systolic dysfunction (ejection fraction <40%), ACE inhibitors and β-blockers are recommended for initial therapy. Aldosterone antagonists (mineralocorticoid receptor antagonists) may be combined in treatment for patients with a recent cardiovascular hospitalization, acute myocardial infarction, elevated B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide level, or New York Heart Association (NYHA) Class II-IV symptoms. Careful monitoring for hyperkalemia is recommended when combining an aldosterone antagonist with ACE inhibitor or ARB treatment. Other diuretics are recommended as additional therapy if needed. Beyond considerations of BP control, doses of ACE inhibitors or ARBs should be titrated to those reported to be effective in trials unless adverse effects become manifest. • An ARB is recommended if ACE inhibitors are not tolerated.

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	• A combination of hydralazine and isosorbide dinitrate is recommended if ACE inhibitors and ARBs are contraindicated or not tolerated.
	• For hypertensive patients whose BP is not controlled, an ARB may be combined with an ACE inhibitor and other antihypertensive drug treatment. Careful monitoring should be used if combining an ACE inhibitor and an ARB because of potential adverse effects such as hypotension, hyperkalemia, and worsening renal function. Additional therapies may also include dihydropyridine CCBs.
	• An angiotensin receptor-neprilysin inhibitor (ARNI) should be used in place of an ACE inhibitor or ARB for patients with HFrEF (<40%) who remain symptomatic despite treatment with appropriate dose of guideline directed HF therapy. Eligible patients must have a serum potassium <5.2 mmol/L, an eGFR ≤30 mL/min/1.73m^2 and close surveillance of serum potassium and creatinine.
	
	<u>Treatment of hypertension in association with stroke</u>
	• BP management in acute ischemic stroke (onset to 72 hours)
	  o Please refer to Stroke Best Practice recommendations.
	• BP management after acute ischemic stroke
	  o Strong consideration should be given to the initiation of antihypertensive therapy after the acute phase of a stroke or transient ischemic attack.
	  o After the acute phase of a stroke, BP-lowering treatment is recommended to a target of consistently <140/90 mmHg.
	  o Treatment with an ACE inhibitor and thiazide/thiazide-like diuretic combination is preferred.
	  o For patients with stroke, the combination of an ACE inhibitor and ARB is not recommended.
	• BP management in hemorrhagic stroke (onset to 72 hours)
	  o Please refer to Stroke Best Practice recommendations.
	
	<u>Treatment of hypertension in association with LVH</u>
	• Hypertensive patients with LVH should be treated with antihypertensive therapy to decrease the rate of subsequent cardiovascular events.
	• The choice of initial therapy can be influenced by the presence of LVH. Initial therapy can be drug treatment using ACE inhibitors, ARBs, long-acting CCBs, or thiazide/thiazide-like diuretics. Direct arterial vasodilators such as hydralazine or minoxidil should not be used.
	
	<u>Treatment of hypertension in association with nondiabetic chronic kidney disease</u>
	• Individualize BP targets in patients with chronic kidney disease. Consider intensive targets (SBP <120 mmHg) in appropriate patients.
	• For patients with hypertension and proteinuric chronic kidney disease (urinary protein >150 mg per 24 hours or albumin to creatinine ratio >30 mg/mmol), initial therapy should be an ACE inhibitor or an ARB if there is intolerance to ACE inhibitors.
	• In most cases, combination therapy with other antihypertensive agents might be needed to reach target BP levels.
	• The combination of an ACE inhibitor and ARB is not recommended for patients with nonproteinuric chronic kidney disease.
	
	<u>Treatment of hypertension in association with renovascular disease</u>
	• Patients with hypertension attributable to atherosclerotic renal artery stenosis should be primarily medically managed because renal angioplasty and stenting offers no benefit over optimal medical therapy alone.
	• Renal artery angioplasty and stenting for atherosclerotic hemodynamically significant renal artery stenosis could be considered for patients with uncontrolled hypertension resistant to maximally tolerated pharmacotherapy,

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	progressive renal function loss, and acute pulmonary edema. • Patients with confirmed renal fibromuscular dysplasia (FMD) should be referred to a hypertension specialist. • Renal artery angioplasty without stenting is recommended for treatment of FMD-related renal artery stenosis. Stenting is not recommended unless needed because of a periprocedural dissection. Surgical revascularization should be considered in cases of complex lesions less amendable to angioplasty, stenosis associated with complex aneurysm, and restenosis despite two unsuccessful attempts of angioplasty. <u>Treatment of hypertension in association with diabetes mellitus</u> • Persons with diabetes mellitus should be treated to attain SBP of <130 mmHg and DBP of <80 mmHg. • For persons with cardiovascular or kidney disease, including microalbuminuria, or with cardiovascular risk factors in addition to diabetes and hypertension, an ACE inhibitor or an ARB is recommended as initial therapy. • For persons with diabetes and hypertension not included in other guidelines in this section, appropriate choices include (in alphabetical order): ACE inhibitors, ARBs, dihydropyridine CCBs, and thiazide/thiazide-like diuretics. • If target BP levels are not achieved with standard-dose monotherapy, additional antihypertensive therapy should be used. For persons in whom combination therapy with an ACE inhibitor is being considered, a dihydropyridine CCB is preferable to a thiazide/thiazide-like diuretic. <u>Resistant hypertension</u> • Resistant hypertension is defined as BP above target despite three or more BP-lowering drugs at optimal doses preferably including a diuretic (and usually a renin-angiotensin-aldosterone system blocker and a CCB. • Accurate office and out-of-office BP measurement is essential. • Other reasons for apparent resistant hypertension should be eliminated before diagnosing true resistant hypertension, including nonadherence, white coat effect, and secondary hypertension. • Pharmacotherapy with the additional use of spironolactone, bisoprolol, doxazosin, amiloride, eplerenone, or clonidine with the baseline regimen decreases BP significantly, with the greatest BP-lowering shown with spironolactone. • Patients with resistant hypertension should be referred to providers with expertise in diagnosis and management of hypertension. <u>Hypertension and pediatrics</u> • BP should be measured regularly in children three years of age or older; the auscultatory method is the gold-standard at present. • Initial therapy should be monotherapy, with an ACE inhibitor or ARB (not first-line in black children), or a long-acting dihydropyridine CCB. • The treatment t goal is systolic and diastolic office BP and/or ABPM < 95th percentile or <90th percentile in children with risk factors or target organ damage. • Complex cases should be referred to an expert in pediatric hypertension. <u>Hypertension and pregnancy</u> • Up to 7% of pregnancies are complicated by a hypertensive disorder of pregnancy, and approximately 5% of women will have chronic hypertension when they become pregnant. • The prevalence of hypertension in pregnancy is expected to increase with women becoming pregnant later in their reproductive years and the increasing prevalence of cardiovascular comorbidities such as increased preconception body mass

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	index and maternal diabetes. • The possibility of pregnancy should be considered when managing women with hypertension who are of reproductive age. • Preconception counselling should be offered to all women with hypertension who are considering pregnancy. • ACE inhibitor and ARB therapy should be avoided before conception and during pregnancy unless there is a compelling indication for their use (i.e., proteinuric kidney disease). • Hypertension during pregnancy can increase the risk of adverse maternal and fetal outcomes, including an increased risk of preeclampsia, placental abruption, prematurity, small for gestational age infants, stillbirth, and maternal renal and retinal injury, thus generally requires involvement of an interdisciplinary team including obstetrical care providers. • Antihypertensive therapy is recommended for average SBP measurements of ≥140 mmHg or DBP measurements of ≥90 mmHg in pregnant women with chronic hypertension, gestational hypertension, or preeclampsia. Initial antihypertensive therapy should be monotherapy from the following first-line drugs: oral labetalol, oral methyldopa, long-acting oral nifedipine, or other oral b-blockers (acebutolol, metoprolol, pindolol, and propranolol). Other antihypertensive drugs can be considered as second-line drugs including: clonidine, hydralazine, and thiazide diuretics. • Women with severe hypertension with SBP ≥160 mmHg or DBP ≥110 mmHg in pregnancy or postpartum require urgent antihypertensive therapy because it is considered an obstetrical emergency. • Antihypertensive drugs used in breastfeeding women include: labetalol, methyldopa, long-acting nifedipine, enalapril, or captopril.
European Society of Hypertension: **2023 Guidelines for the management of arterial hypertension (2023)**[32]	General recommendations for antihypertensive drug treatment • BP lowering should be prioritized over the selection of specific antihypertensive drug classes because treatment benefit largely originates from BP reduction. • Five major drug classes including, ACE inhibitors, ARBs, β-blockers, CCBs, and Thiazide/Thiazide-like diuretics have effectively reduced blood pressure and cardiovascular events in randomized controlled trials. These drugs and their combinations are recommended as the basis of antihypertensive treatment strategies. • Initiation of therapy with a two-drug combination is recommended for most hypertensive patients. Preferred combinations should comprise a RAS blocker (either an ACE inhibitor or an ARB) with a CCB or thiazide/thiazide-like diuretic. Other combinations of the five major drug classes can be used. • Initiation with monotherapy can be considered in patients with: grade 1 hypertension and low-risk if BP is only marginally elevated (less than 150 mmHg SBP and 95 mmHg DBP) high-normal BP and very high cardiovascular risk, frailty and/or and advance age. • If BP is not controlled with the initial two-drug combination by using the maximum recommended and tolerated dose of the respective components, treatment should be increased to a three-drug combination, usually a RAS blocker plus CCB plus thiazide/thiazide-like diuretic. • If BP is not controlled with a three-drug combination by using the maximum recommended and tolerated dose of the respective components, it is recommended to extend treatment according to the recommendations for resistant hypertension. • The use of single pill combinations should be preferred at any treatment step (i.e. during initiation of therapy with a two-drug combination and at any other step of treatment). • β-blocker should be used at initiation of therapy or at any treatment step as guideline-directed medical therapy (e.g., heart failure with reduced ejection

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	fraction, anti-ischemic therapy in chronic coronary syndromes, heart rate control in atrial fibrillation). • β-blockers can be considered in the presence of several other conditions in which their use can be favorable. • The combination of two RAS blockers is not recommended due to increased risk of adverse events, in particular AKI. True-resistant hypertension • In resistant hypertension, it is recommended to reinforce lifestyle measures. • Drugs that can be considered as additional therapy in patients with resistant hypertension are preferably spironolactone (or other MRA), or β-blocker or Alpha-1 blockers or centrally acting agents (clonidine), or amiloride. • Thiazide/thiazide-like diuretics are recommended in resistant hypertension if estimated eGFR is ≥30 mL/min/1.73m^2. • Loop diuretics may be considered in patients with an estimated eGFR < 45 mL/min/1.73m^2 and should be used if eGFR falls below 30 mL/min/1.73m^2. • Chlorthalidone (12.5 to 25 mg once daily) could be used with or without a loop diuretic if eGFR is <30 mL/min/1.73m^2. • Renal deprivation can be considered as an additional treatment option in patients with resistant hypertension if eGFR is >40 mL/min/1.73m^2. • Patients with resistant hypertension should be followed very closely. Follow-up includes periodical ambulatory blood pressure monitoring and assessment of hypertension-mediated organ damage, particularly kidney function and serum potassium levels. Regular use of home blood pressure monitoring and monitoring of drug adherence are desirable.
National Institute for Health and Clinical Excellence: **Hypertension in adults: diagnosis and management (2019)**[33]	Choosing antihypertensive drug treatment (for people with or without type II diabetes) • Where possible, recommend treatment with drugs taken only once a day. • Prescribe non-proprietary drugs where these are appropriate and minimize cost. • Offer people with isolated systolic hypertension (systolic blood pressure ≥160 mmHg) the same treatment as people with both raised systolic and diastolic blood pressure. • Offer antihypertensive drug treatment to women of child-bearing potential with diagnosed hypertension in line with recommendations in this guideline. For women considering pregnancy or who are pregnant or breastfeeding, manage hypertension in line with the recommendations on Management of pregnancy with chronic hypertension and Breastfeeding in 'Hypertension in pregnancy'. • When choosing antihypertensive drug treatment for adults of black African or African-Caribbean family origin, consider an angiotensin II receptor blocker, in preference to an angiotensin-converting enzyme inhibitor. Step one treatment • Patients <55 years of age should be offered a step one antihypertensive with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). • Offer an ACE inhibitor or an ARB to adults starting step 1 antihypertensive treatment who have type II diabetes and are of any age or family origin or those aged <55 years but not of black African or African-Caribbean family origin. • If an ACE inhibitor is not tolerated, offer an ARB. • Do not combine an ACE inhibitor with an ARB for the treatment of hypertension. • Offer a calcium channel blocker (CCB) to adults starting step 1 antihypertensive treatment who are >55 years of age and do not have diabetes and are of black African or African-Caribbean family origin and do not have type II diabetes and

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	of any age. • If a CCB is not suitable, for example because of edema or intolerance, or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic. • If diuretic treatment is to be initiated or changed, offer a thiazide‑like diuretic, such as indapamide in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide. • For adults with hypertension who are already receiving treatment with bendroflumethiazide or hydrochlorothiazide, who have stable, well-controlled blood pressure, continue with their treatment. <u>Step two treatment</u> • Before considering next step treatment for hypertension discuss with the person if they are taking their medicine as prescribed and support adherence in line with NICE's guideline on "Medicines adherence: involving patients decisions about prescribed medicines and supporting adherence". • If hypertension is not controlled with a step one treatment of an ACE inhibitor or ARB, offer choice of one of the following drugs in addition to the step one treatment: a CCB or a thiazide-like diuretic. • If hypertension is not controlled in adults taking step one treatment of a CCB, offer the choice of one of the following drugs in addition to the step one treatment: an ACE inhibitor or an ARB or a thiazide-like diuretic. • If hypertension is not controlled in adults of black African or African–Caribbean family origin who do not have type 2 diabetes taking step one treatment, consider an ARB, in preference to an ACE inhibitor, in addition to step one treatment. <u>Step three treatment</u> • Before considering step three treatment, review the person's medications to ensure they are being taken at the optimal doses and discuss adherence (see recommendation under step two). • If hypertension is not controlled in adults taking step two treatment, offer a combination of an ACE inhibitor or ARB and a CCB and a thiazide-like diuretic. <u>Step four treatment</u> • If hypertension is not controlled in adults taking the optimal tolerated doses of an ACE inhibitor or an ARB plus a CCB and a thiazide-like diuretic, regard them as having resistant hypertension. • Before considering further treatment for a person with resistant hypertension, confirm elevated clinic blood pressure measurements using ambulatory or home blood pressure recordings, assess for postural hypotension, and discuss adherence. • For people with confirmed resistant hypertension, consider adding a fourth antihypertensive drug as step four treatment or seeking specialist advice. • Consider further diuretic therapy with low-dose spironolactone for adults with resistant hypertension starting step four treatment who have a blood potassium level of 4.5 mmol/l or less. Use particular caution in people with a reduced estimated glomerular filtration rate because they have an increased risk of hyperkalemia. • When using further diuretic therapy for step four treatment of resistant hypertension, monitor blood sodium and potassium and renal function within one month of starting treatment and repeat as needed thereafter. • Consider an alpha-blocker or beta-blocker for adults with resistant hypertension starting step four treatment who have a blood potassium level of more than 4.5 mmol/l. • If blood pressure remains uncontrolled in people with resistant hypertension

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	taking the optimal tolerated doses of four drugs, seek specialist advice.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in Blacks (2010)**[34]	• To attain and maintain blood pressure (BP) below target levels, multiple antihypertensive drugs will be required in most hypertensive blacks. • Use of two-drug combination therapy when SBP is >15 mm Hg and/or DBP is >10 mm Hg above goal levels is increasingly recommended as first-line therapy. • Two-drug regimens have generally contained a thiazide-type diuretic; however, the combination of a calcium channel blocker (CCB) with either an ACE inhibitor or an ARB has been shown equally efficacious in BP lowering but with demonstrated superiority (CCB+ACE) for hard clinical outcomes compared with the same ACE inhibitor plus a thiazide-type diuretic. • In secondary prevention patients, the combination therapy should include a drug(s) with the appropriate compelling indications. • Certain classes of antihypertensive medications, specifically diuretics and CCBs, lower BP on average more than β-blockers and renin-angiotensin system (RAS) blockers in black patients when used as monotherapies. • In the absence of compelling indications, when BP is near goal levels, monotherapy with a diuretic or a CCB is preferred. • Lifestyle modifications should be initiated in all patients with hypertension, whether or not pharmacotherapy is planned. • ACE inhibitors or ARBs are recommended as alternative monotherapy options in the treatment of hypertension in blacks. The rationale for their lower tier monotherapy recommendation is because they have consistently achieved lesser average reductions in BP relative to that observed with monotherapy using either a diuretic or CCB.
Kidney Disease Improving Clinical Outcomes Group: **KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease (2021)**[35]	<u>Blood pressure measurement</u> • The Work Group recommends standardized office blood pressure (BP) measurement in preference to routine office BP measurements for the management of high BP in adults. • The Work Group suggests that out-of-office BP measurements with ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM) be used to complement standardized office BP readings for the management of high BP. <u>Lifestyle interventions for lowering BP in patients with chronic kidney disease (CKD) not receiving dialysis</u> • The Work Group suggests targeting a sodium intake <2 grams of sodium per day (or <90 mmol of sodium per day, or <5 grams of sodium chloride per day) in patients with high BP and CKD. • The Work Group suggests that patients with high BP and CKD be advised to undertake moderate-intensity physical activity for a cumulative duration of at least 150 minutes per week, or to a level compatible with their cardiovascular and physical tolerance. <u>BP management in patients with CKD, with or without diabetes, not receiving dialysis</u> • The Work Group suggests that adults with high BP and CKD be treated with a target systolic BP (SBP) of <120 mmHg, when tolerated, using standardized office BP measurement. • The Work Group recommends starting renin-angiotensin-system inhibitors (RASi) (angiotensin-converting enzyme inhibitor [ACEi] or angiotensin II receptor blocker [ARB]) for people with high BP, CKD, and severely increased albuminuria without diabetes. • The Work Group suggests starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately increased albuminuria without diabetes. • The Work Group recommends starting RASi (ACEi or ARB) for people with

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	high BP, CKD, and moderately-to-severely increased albuminuria with diabetes. • The Work Group recommends avoiding any combination of ACEi, ARB, and direct renin inhibitor (DRI) therapy in patients with CKD, with or without diabetes. BP management in kidney transplant recipients • Treat adult kidney transplant recipients with high BP to a target BP of <130 mmHg systolic and <80 mmHg diastolic using standardized office BP measurement. • The Work Group recommends that a dihydropyridine calcium channel blocker (CCB) or an ARB be used as the first-line antihypertensive agent in adult kidney transplant recipients. BP management in children with CKD • The Work Group suggests that in children with CKD, 24-hour mean arterial pressure by ABPM should be lowered to <50th percentile for age, sex, and height.
American College of Cardiology/ American Heart Association Task Force: **Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults (2017)**[36]	Initiation of Blood Pressure (BP) Treatment for Overall Cardiovascular Disease (CVD) Risk • Use of BP-lowering medications is recommended for secondary prevention of recurrent CVD events in patients with clinical CVD and an average systolic blood pressure (SBP) ≥130 mmHg or an average diastolic blood pressure (DBP) of ≥80 mmHg and for primary prevention in adults with an estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk of ≥10% and an average SBP of ≥130 mmHg or an average ≥80 mmHg. • Use of BP-lowering medication is recommended for primary prevention of CVD in adults with no history of CVD and with an estimated 10-year ASCVD risk <10% and an SBP of ≥140 mmHg or a DBP of ≥90 mmHg. • Simultaneous use of an angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), and/or renin inhibitor is potentially harmful and is not recommended to treat adults with hypertension. • For adults with confirmed hypertension and known CVD or 10-year ASCVD risk of ≥10%, a BP target <130/80 mmHg is recommended. For adults with confirmed hypertension without additional markers of increased CVD risk, a BP target <130/80 mmHg may be reasonable. • For initiation of antihypertensive drug therapy, first-line agents include thiazide diuretics, calcium channel blockers (CCBs), and ACE inhibitors or ARBs. • Initiation of antihypertensive drug therapy with two first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended in adults with stage 2 hypertension and an average BP >20/10 mmHg above their BP target. • Initiation of antihypertensive drug therapy with a single antihypertensive drug is reasonable in adults with stage 1 hypertension and BP goal <130/80 mmHg with dosage titration and sequential addition of other agents to achieve the BP target. Stable Ischemic Heart Disease (SIHD) • In adults with SIHD and hypertension, a BP target <130/80 is recommended. • Adults with SIHD and hypertension (BP ≥130/80 mmHg) should be treated with medications [e.g., guideline-directed medical therapy (GDMT) beta-blockers, ACE inhibitors, or ARBs] for compelling indications [e.g., previous myocardial infarction (MI), stable angina] as first-line therapy, with the addition of other drugs (e.g., dihydropyridine CCBs, thiazide diuretics, and/or mineralocorticoid receptor antagonists) as needed to further control hypertension. • In adults with SIHD with angina and persistent uncontrolled hypertension, the addition of dihydropyridine CCBs to GDMT beta-blockers is recommended. • In adults who have had a MI or acute coronary syndrome, it is reasonable to

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	continue GDMT beta-blockers beyond three years as long-term therapy for hypertension. • Beta-blockers and/or CCBs might be considered to control hypertension in patients with coronary artery disease (CAD) had an MI more than three years ago and have angina. <u>Heart Failure</u> • In adults with increased risk of HF, the optimal BP in those with hypertension should be <130 mmHg. • Adults with HFrEF and hypertension should be prescribed GDMT titrated to attain a BP <130/80 mmHg. • Non-dihydropyridine CCBs are not recommended in the treatment of hypertension in adults with HFrEF. • In adults with HFpEF who present with symptoms of volume overload, diuretics should be prescribed to control hypertension. • Adults with HFpEF and persistent hypertension after management of volume overload should be prescribed ACE inhibitors or ARBs and beta-blockers titrated to attain SBP <130 mmHg. <u>CKD</u> • Adults with hypertension and CKD should be treated to a BP goal <130/80 mmHg. • In adults with hypertension and CKD [stage 3 or higher or stage 1 or 2 with albuminuria (≥300 mg/d, or ≥300 mg/g albumin-to-creatinine ratio or the equivalent in the first morning void)], treatment with an ACE inhibitor is reasonable to slow kidney disease progression. Treatment with an ARB may be reasonable if an ACE inhibitor is not tolerated. • After kidney transplantation, it is reasonable to treat patients with hypertension to a BP goal <130/80 mmHg and with a CCB on the basis of improved glomerular filtration rate (GFR) and kidney survival. <u>Cerebrovascular Disease</u> • In adults with intracerebral hemorrhage (ICH) who present with SBP >220 mmHg, it is reasonable to use continuous intravenous (IV) drug infusion and close BP monitoring to lower levels. Immediate lowering of SBP to <140 mmHg in adults with spontaneous ICH who present within six hours of the acute event and have an SBP between 150 mmHg and 220 mmHg is not of benefit to reduce death or severe disability and can be potentially harmful. • Adults with acute ischemic stroke and elevated BP who are eligible for treatment with IV tissue plasminogen activator (tPA) should have their BP slowly lowered to <185/110 mmHg before thrombolytic therapy is initiated. • In adults with an acute ischemic stroke, BP should be <185/110 mmHg before administration of IV tPA and should be maintained below 180/105 mmHg for at least the first 24 hours after initiation drug therapy. • Starting or restarting antihypertensive therapy during hospitalization in patients with BP >140/90 mmHg who are neurologically stable is safe and reasonable to improve long-term BP control, unless contraindicated. • In patient with BP ≥220/120 mmHg who did not receive IV alteplase or endovascular treatment and have no comorbid conditions requiring acute antihypertensive treatment, the benefit of initiating or reinitiating treatment of hypertension within the first 48 to 72 hours is uncertain. It might be reasonable to lower BP by 15% during the first 24 hours after onset of stroke. In patients with BP <220/120 mmHg with the same conditions, initiating or reinitiating treatment of hypertension within the first 48 to 72 hours after an acute ischemic stroke is not effective to prevent death or dependency.

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	• Adults with previously treated stroke or transient ischemic attack should be restarted on antihypertensive treatment after the first few days of the index event to reduce the risk of recurrent stroke and other vascular events. Treatment with a thiazide diuretic, ACE inhibitor, or ARB, or combination treatment consisting of a thiazide diuretic plus ACE inhibitor, is useful. • Adults not previously treated for hypertension who experienced a stroke or transient ischemic attack and have an established BP ≥140/90 mmHg should be prescribed antihypertensive treatment a few days after the index event to reduce the risk of recurrent stroke and other vascular event. • For adults who experience a stroke or transient ischemic attack, selection of specific drugs should be individualized on the basis of patient comorbidities and agent pharmacological class. • For adults who experience a stroke or transient ischemic attack, a BP goal <130/80 mmHg may be reasonable. • For adults with a lacunar stroke, a target SBP goal <130 mmHg may be reasonable. • In adults previously untreated for hypertension who experience an ischemic stroke or transient ischemic attack and have an SBP <140 mmHg and a DBP <90 mmHg, the usefulness of initiating antihypertensive treatment is not well established. <u>Peripheral Artery Disease (PAD)</u> • Adults with hypertension and PAD should be treated similarly to patients with hypertension without PAD. <u>Diabetes Mellitus (DM)</u> • In adults with DM and hypertension, antihypertensive drug treatment should be initiated at a BP of ≥130/80 mmHg with a treatment goal <130/80 mmHg. • In adults with DM and hypertension, all first-line classes of antihypertensive agents (i.e., diuretics, ACE inhibitors, ARBs, and CCBs) are useful and effective. • In adults with DM and hypertension, ACE inhibitors or ARBs may be considered in the presence of albuminuria. <u>Atrial Fibrillation, Valvular Heart Disease, and Aortic disease</u> • Treatment of hypertension can be useful for prevention of recurrence of AF. • In adults with asymptomatic aortic stenosis, hypertension should be treated with pharmacotherapy, starting at a low dose and gradually titrating upward as needed. • In patients with chronic aortic insufficiency, treatment of systolic hypertension with agents that do not slow the heart rate (i.e., avoid beta-blockers) is reasonable. • Beta-blockers are recommended as the preferred antihypertensive agents in patients with hypertension and thoracic aortic disease. <u>Racial and Ethnic Differences in Treatment</u> • In black adults with hypertension but without HF or CKD, including those with DM, initial antihypertensive treatment should include a thiazide-type diuretic or CCB. Two or more antihypertensive medications are recommended to achieve a BP target <130/80 mmHg in most adults with hypertension, especially in black adults with hypertension. <u>Pregnancy</u> • Women with hypertension who become pregnant, or are planning to become pregnant, should be transitioned to methyldopa, nifedipine, and/or labetalol during pregnancy. • Women with hypertension who become pregnant should not be treated with ACE

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	inhibitors, ARBs, or direct renin inhibitors. Older Persons • Treatment of hypertension with an SBP treatment goal <130 mmHg is recommended for noninstitutionalized ambulatory community-dwelling adults (≥65 years of age) with an average SBP of ≥130 mmHg. • For older adults (≥65 years of age) with hypertension and a higher burden of comorbidity and limited life expectancy, clinical judgment, patient preference, and a team-based approach to assess risk/benefit is reasonable for decisions regarding intensity of BP lowering and choice of antihypertensive drugs. Hypertensive Crises • In adults with a hypertensive emergency, admission to an intensive care unit is recommended for continuous monitoring of BP and target organ damage and for parenteral administration of an appropriate agent. • For adults with a compelling condition (i.e., aortic dissection, severe pre-eclampsia or eclampsia, or pheochromocytoma crisis), SBP should be reduced to <140 mmHg during the first hour and to <120 mmHg in aortic dissection. • For adults without a compelling condition, SBP should be reduced by no more than 25% within the first hours; then, if stable, to 160/100 mmHg within the next two to six hours; and then cautiously to normal during the following 24 to 48 hours. Cognitive Decline and Dementia • In adults with hypertension, BP lowering is reasonable to prevent cognitive decline and dementia. Patients Undergoing Surgical Procedures • In patients with hypertension undergoing major surgery who have been on beta-blockers chronically, beta-blockers should be continued. • In patients with hypertension undergoing planned elective major surgery, it is reasonable to continue medical therapy for hypertension until surgery. • In patients with hypertension undergoing major surgery, discontinuation of ACE inhibitors or ARBs perioperatively may be considered. • In patients with planned elective major surgery and SBP ≥180 mmHg or DBP ≥110 mmHg, deferring surgery may be considered. • For patients undergoing surgery, abrupt pre-operative discontinuation of beta-blockers or clonidine is potentially harmful. • Beta-blockers should not be started on the day of surgery in beta-blocker-naïve patients. • Patients with intraoperative hypertension should be managed with IV medications until such time as oral medications can be resumed.
American Diabetes Association: **Standards of Medical Care in Diabetes (2023)**[37]	Hypertension/blood pressure control • Blood pressure should be measured at every routine visit. When possible, patients found to have elevated blood pressure (systolic blood pressure 120 to 129 mmHg and diastolic <80 mmHg) should have blood pressure confirmed using multiple readings, including measurements on a separate day, to diagnose hypertension. Patients with blood pressure ≥180/110 and cardiovascular disease could be diagnosed with hypertension at a single visit. • All hypertensive patients with diabetes should monitor their blood pressure at home. • For patients with diabetes and hypertension, blood pressure targets should be individualized through a shared decision-making process that addresses cardiovascular risk, potential adverse effects of antihypertensive medications, and patient preferences.

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	• Individuals with diabetes and hypertension qualify for antihypertensive drug therapy when the blood pressure is persistently elevated ≥130/80 mmHg. The on-treatment target blood pressure goal is <130/80 mmHg, if it can be safely attained. • In pregnant patients with diabetes and preexisting hypertension, a blood pressure target of 110 to 135/85 is suggested in the interest of reducing the risk for accelerated maternal hypertension and minimizing impaired fetal growth. • For patients with blood pressure >120/80, lifestyle intervention consists of weight loss when indicated, a Dietary Approaches to Stop Hypertension (DASH)-style eating pattern including reducing sodium and increasing potassium intake, moderation of alcohol intake, and increased physical activity. • Patients with confirmed office-based blood pressure ≥130/80 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of pharmacologic therapy to achieve blood pressure goals. • Patients with confirmed office-based blood pressure ≥160/100 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of two drugs or a single pill combination of drugs demonstrated to reduce cardiovascular events in patients with diabetes. • Treatment for hypertension should include drug classes demonstrated to reduce cardiovascular events in patients with diabetes (ACE inhibitors, angiotensin receptor blockers, thiazide-like diuretics, or dihydropyridine calcium channel blockers). ACE inhibitors or angiotensin receptor blockers are recommended first-line therapy for hypertension in people with diabetes and coronary artery disease. • Multiple-drug therapy is generally required to achieve blood pressure targets (but not a combination of ACE inhibitors and angiotensin receptor blockers). • An ACE inhibitor or angiotensin receptor blocker, at the maximum tolerated dose indicated for blood pressure treatment, is the recommended first-line treatment for hypertension in patients with diabetes and urinary albumin–to–creatinine ratio ≥300 mg/g creatinine or 30 to 299 mg/g creatinine. If one class is not tolerated, the other should be substituted. • For patients treated with an ACE inhibitor, angiotensin receptor blocker, or diuretic, serum creatinine/estimated glomerular filtration rate and serum potassium levels should be monitored at least annually. • Patients with hypertension who are not meeting blood pressure targets on three classes of antihypertensive medications (including a diuretic) should be considered for mineralocorticoid receptor antagonist therapy. <u>Chronic kidney disease</u> • At least once a year, assess urinary albumin (e.g., spot urinary albumin–to–creatinine ratio) and estimated glomerular filtration rate in patients with type 1 diabetes with duration of five or more years and in all patients with type 2 diabetes. • In people with established diabetic kidney disease, urinary albumin (e.g., spot urinary albumin-to-creatinine ratio) and estimated glomerular filtration rate should be monitored one to four times per year depending on the stage of the disease. Optimize glucose control to reduce the risk or slow the progression of chronic kidney disease (CKD). • For patients with type 2 diabetes and diabetic kidney disease, use of a sodium-glucose cotransporter 2 inhibitor in patients with an estimated glomerular filtration rate ≥20 mL/min/1.73 m^2 and urinary albumin ≥200 mg/g creatinine is recommended to reduce CKD progression and cardiovascular events. • For patients with type 2 diabetes and diabetic kidney disease, use of a sodium–glucose cotransporter 2 inhibitor is recommended to reduce chronic kidney disease progression and cardiovascular events in patients with an estimated

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	glomerular filtration rate ≥20 mL/min/1.73 m^2 and urinary albumin ranging from normal to 200 mg/g creatinine. • In people with type 2 diabetes and diabetic kidney disease, consider use of sodium–glucose cotransporter 2 inhibitors (if estimated glomerular filtration rate is ≥20 mL/min/1.73 m^2), a glucagon-like peptide 1 agonist, or a nonsteroidal mineralocorticoid receptor antagonist (if estimated glomerular filtration rate is ≥25 mL/min/1.73 m^2) additionally for cardiovascular risk reduction. • In people with chronic kidney disease and albuminuria who are at increased risk for cardiovascular events or chronic kidney disease progression, a nonsteroidal mineralocorticoid receptor antagonist shown to be effective in clinical trials is recommended to reduce chronic kidney disease progression and cardiovascular events. • Optimize blood pressure control and reduce blood pressure variability to reduce the risk or slow the progression of CKD. • Do not discontinue renin-angiotensin system blockade for minor increases in serum creatinine (≤30%) in the absence of volume depletion. • For people with nondialysis-dependent stage 3 or higher CKD, dietary protein intake should be a maximum of 0.8 g/kg body weight per day (the recommended daily allowance). For patients on dialysis, higher levels of dietary protein intake should be considered, since protein energy wasting is a major problem in some dialysis patients. • In nonpregnant patients with diabetes and hypertension, either an ACE inhibitor or an angiotensin receptor blocker is recommended for those with modestly elevated urinary albumin–to–creatinine ratio (30 to 299 mg/g creatinine) and is strongly recommended for those with urinary albumin–to–creatinine ratio ≥300 mg/g creatinine and/or estimated glomerular filtration rate <60 mL/min/1.73 m^2. • Periodically monitor serum creatinine and potassium levels for the development of increased creatinine and hyperkalemia when ACE inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists are used, or hypokalemia when diuretics are used. • An ACE inhibitor or an angiotensin receptor blocker is not recommended for the primary prevention of CKD in patients with diabetes who have normal blood pressure, normal urinary albumin–to–creatinine ratio (<30 mg/g creatinine), and normal estimated glomerular filtration rate. • Patients should be referred for evaluation by a nephrologist if they have continuously increasing urinary albumin levels and/or continuously decreasing estimated glomerular filtration rate and an estimated glomerular filtration rate <30 mL/min/1.73 m^2. • Promptly refer to a nephrologist for uncertainty about the etiology of kidney disease, difficult management issues, and rapidly progressing kidney disease.

*Agent is not available in the United States.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the angiotensin-converting enzyme inhibitors are noted in Tables 3 and 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Angiotensin-Converting Enzyme Inhibitors[3-17]

Indication(s)	Single Entity Agents									
	Benaze-pril	Capto-pril	Enala-pril	Fosino-pril	Lisino-pril	Moexi-pril	Perindo-pril	Quina-pril	Rami-pril	Trandola-pril
Cardiovascular Risk Reduction										
In patients 55 years or older at high risk of developing a major cardiovascular event because of a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes that is accompanied by at least one other cardiovascular risk factor to reduce the risk of myocardial infarction, stroke, or death from cardiovascular causes									✔	
Stable coronary artery disease to reduce the risk of cardiovascular mortality or nonfatal myocardial infarction							✔			
Diabetic Nephropathy										
Treatment of diabetic nephropathy in patients with type 1 insulin-dependent diabetes and retinopathy		✔								
Heart Failure										
Congestive heart failure		✔ *	✔ *							
Heart failure				✔ †	✔ ‡			✔ †		
Hypertension										
Hypertension	✔ §	✔ ‖	✔ ‖	✔ §	✔ ‖	✔ §	✔ ‖	✔ §	✔ §	✔ ‖
Left Ventricular Dysfunction										
Decrease the rate of the development of overt heart failure and decrease the incidence of hospitalization for heart failure in clinically stable asymptomatic patients with left ventricular dysfunction (ejection fraction ≤35%)			✔							
Myocardial Infarction										
Hemodynamically stable patients within 24 hours of acute myocardial infarction to improve survival					✔					
Improve survival following myocardial infarction in clinically stable patients with left ventricular dysfunction manifested as an ejection fraction ≤40%		✔								

Indication(s)	Single Entity Agents									
	Benaze-pril	Capto-pril	Enala-pril	Fosino-pril	Lisino-pril	Moexi-pril	Perindo-pril	Quina-pril	Rami-pril	Trandola-pril
and to reduce the incidence of overt heart failure and subsequent hospitalizations for congestive heart failure in these patients										
Stable patients who have demonstrated clinical signs of congestive heart failure within the first few days after sustaining acute myocardial infarction									✔	
Stable patients who have evidence of left ventricular systolic dysfunction or who are symptomatic from congestive heart failure within the first few days after sustaining acute myocardial infarction										✔

*Usually in combination with diuretics and digitalis.
† As adjunctive therapy when added to conventional therapy including diuretics with or without digitalis.
‡ As adjunctive therapy in patients who are not responding adequately to diuretics and digitalis.
§ May be used alone or in combination with thiazide diuretics.
‖ May be used alone or in combination with other antihypertensive agents.

Table 4. FDA-Approved Indications for the Angiotensin-Converting Enzyme Inhibitors[3-17]

Indication(s)	Combination Products					
	Benazepril and HCTZ	Captopril and HCTZ	Enalapril and HCTZ	Fosinopril and HCTZ	Lisinopril and HCTZ	Quinapril and HCTZ
Hypertension						
Hypertension	✔ *	✔	✔ *	✔ *	✔ *	✔ *

*This fixed combination product is not indicated for the initial therapy of hypertension.
HCTZ=hydrochlorothiazide

IV. Pharmacokinetics

The pharmacokinetic parameters of the angiotensin-converting enzyme inhibitors are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Angiotensin-Converting Enzyme Inhibitors[18]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Benazepril	37	96.7	Liver, extensive (% not reported)	Renal (33) Bile (12)	22*
Captopril	70 to 75	25 to 30	Liver (50)	Renal (95)	1.9†
Enalapril	60	50 to 60	Liver (70)	Renal (61) Feces (33)	11*
Fosinopril	30 to 36	89 to 100	Liver, extensive (% not reported)	Renal (44) Feces (46)	12*
Lisinopril	25	Minimal (% not reported)	Liver (7)	Renal (29) Feces (69)	12†
Moexipril	13 to 22	50 to 70	Liver, extensive (% not reported)	Renal (13) Feces (50)	2 to 10*
Perindopril	20 to 30	60	Liver (88 to 96)	Renal (75) Feces (25)	3 to 10*
Quinapril	50	97	Liver, extensive (% not reported)	Renal (50 to 60) Feces (33)	2 to 25*
Ramipril	60	73	Liver, extensive (% not reported)	Renal (40 to 60) Feces (40)	13 to 17*
Trandolapril	10	80	Liver, extensive (% not reported)	Feces (66) Renal (33)	16 to 24*
Combination Products					
Benazepril and HCTZ	37/70	96.7/40 to 70	Liver, extensive (% not reported)/ not reported	Feces (11 to 12/ Renal (70)	22*/10
Captopril and HCTZ	70 to 75/70	25 to 30/ not reported	Liver (50%)/ not reported	Renal (>95)/ Renal (% not reported)	<3/2.5
Enalapril and HCTZ	60/70	Not reported/40	Not reported/ Liver, minimal (% not reported)	Renal (61)/ Renal (60)	11/5.6 to 14.8
Fosinopril and HCTZ	36/50 to 80	95/67.9	Liver (% not reported)/ Not reported	Not reported/ Renal (61)	Not reported/ 5 to 15
Lisinopril and HCTZ	25/not reported	Not reported/ Not reported	Not reported/ Not reported	Not reported/ Not reported	Not reported/ Not reported
Quinapril and HCTZ	60/50 to 80	97/67.9	Liver (% not reported)/ Not metabolized	Renal (96)/ Renal (61)	2 to 25*/ 4 to 15

*Metabolites
†Parent compound
HCTZ=hydrochlorothiazide

V. Drug Interactions

Major drug interactions with the angiotensin-converting enzyme inhibitors are listed in Table 6.

Table 6. Major Drug Interactions with the Angiotensin-Converting Enzyme Inhibitors[18]

Generic Name(s)	Interaction	Mechanism
ACE inhibitors (benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril)	Potassium-sparing diuretics	Combining ACE inhibitors and potassium-sparing diuretics may result in elevated serum potassium concentrations in certain high-risk patients.
ACE inhibitors (benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril)	Sacubitril	Concurrent use of sacubitril and ACE Inhibitors may result in Increased risk of angioedema.
ACE inhibitors (benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril)	Aliskiren	The risk of hyperkalemia may be increased when ACE inhibitors are combined with aliskiren.
ACE inhibitors (benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril)	Angiotensin II receptor antagonists	The risk of hyperkalemia may be increased when ACE inhibitors are combined with angiotensin II receptor antagonists.
ACE inhibitors (benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril)	Indomethacin	Indomethacin inhibits prostaglandin synthesis. The hypotensive effect of ACE inhibitors may be reduced.
ACE inhibitors (benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril)	NSAIDs and salicylates	NSAIDs and salicylates inhibit prostaglandin synthesis. The hypotensive and vasodilator effects of the ACE inhibitor may be reduced.
ACE inhibitors (benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril)	Potassium preparations	Hyperkalemia, possibly with cardiac arrhythmias or cardiac arrest, may occur with the combination of ACE inhibitors and potassium preparations.
ACE inhibitors (benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril)	Everolimus, sirolimus	Concurrent use of ACE inhibitors and MTOR inhibitors may result in increased risk of angioedema.
ACE inhibitors (benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril)	Trimethoprim	Hyperkalemia, possibly with cardiac arrhythmias or cardiac arrest, may occur with the combination of ACE inhibitors and trimethoprim.
ACE inhibitors	Lithium	Through an unknown mechanism, ACE inhibitors

Generic Name(s)	Interaction	Mechanism
(benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, quinapril, ramipril, trandolapril)		may increase lithium levels, which results in neurotoxicity.
Thiazide diuretics (HCTZ)	Dofetilide	Thiazide diuretics increase potassium excretion. Hypokalemia may occur, increasing the risk of torsades de pointes.
Thiazide diuretics (HCTZ)	Lithium	Thiazide diuretics decrease the renal clearance of lithium which leads to increased serum lithium levels. Lithium toxicity has occurred.
Thiazide diuretics (HCTZ)	Diazoxide	Hyperglycemia may occur with symptoms similar to diabetes. The mechanism is unknown.
Thiazide diuretics (HCTZ)	Digitalis glycosides	Diuretic-induced electrolyte disturbances may predispose the patient to digitalis-induced cardiac arrhythmias.

ACE inhibitor=angiotensin converting enzyme inhibitor, HCTZ=hydrochlorothiazide, HMG CoA=3-hydroxy-3-methyl-glutaryl-CoA, NSAID=nonsteroidal anti-inflammatory drug

VI. Adverse Drug Events

The most common adverse drug events reported with the angiotensin-converting enzyme inhibitors are listed in Tables 7 and 8. The boxed warning for the angiotensin-converting enzyme inhibitors is listed in Table 9.

Table 7. Adverse Drug Events (%) Reported with the Angiotensin-Converting Enzyme Inhibitors-Single Entity Agents[3-18]

Adverse Events	Benazepril	Captopril	Enalapril	Fosinopril	Lisinopril	Moexipril	Perindopril	Quinapril	Ramipril	Trandolapril
Cardiovascular										
Angina	<1	<1	2	<1	-	<1	-	<1	<1 to 3	-
Bradycardia	-	-	<1	<1	<1	-	-	-	<1	<5
Cardiac arrest	-	✔	<1	✔	<1	-	✔	-	✔	-
Cerebrovascular accident	-	✔	<1	<1	<1	<1	<1	<1	<1	-
Chest pain	-	1	2	<2	3	>1	2	2	<1	<1
Hypotension	<1	✔	1 to 7	1 to 4	1 to 10	<1	<1	3	<1	<1
Myocardial infarction	-	<1	<1	<1	<1	<1	<1	<1	<1	-
Orthostatic hypotension	<1	✔	1 to 2	<2	<1	<1	<1	<1	2	-
Palpitations	<1	1	<1	<1	<1	<1	<1	<1	<1	<1
Peripheral edema	<1	-	-	-	<1	>1	-	-	-	-
Rhythm disturbances	-	✔	<1	<1	-	<1	-	<1	-	-
Tachycardia	-	1	<1	<1	<1	-	-	<1	<1	-
Central Nervous System										
Anxiety	<1	-	-	-	-	<1	<1	-	<1	<1
Ataxia	-	✔	<1	-	<1	-	-	-	-	-
Depression	-	✔	<1	<1	-	-	2	<1	<1	-
Dizziness	4	-	1 to 8	2 to 12	5 to 12	4	8	4 to 8	2 to 4	1 to 23
Fatigue	2	-	1 to 3	≥1	3	2	-	3	2	-
Headache	6	-	2 to 5	≥1	4 to 6	>1	24	2	-	-
Insomnia	<1	-	<1	<1	<1	<1	3	<1	<1	<1
Malaise	-	-	-	-	<1	<1	<1	<1	<1	-
Nervousness	<1	✔	<1	-	<1	<1	1	<1	<1	-
Paresthesias	<1	-	<1	<1	<1	-	2	<1	<1	<1
Peripheral edema	<1	-	-	-	-	>1	-	-	-	-
Somnolence/drowsiness	2	✔	<1	<1	<1	<1	1	<1	<1	<1
Vertigo	-	-	2	<1	<1	-	<1	<1	<1 to 2	<1
Dermatologic										
Alopecia	<1	-	<1	-	<1	<1	-	<1	-	-
Diaphoresis	<1	-	<1	<1	<1	<1	<1	<1	<1	-
Erythema multiforme	-	✔	<1	-	-	-	<1	-	<1	-
Exfoliative dermatitis	-	✔	<1	✔	-	-	✔	<1	-	-
Flushing	<1	<1	<1	<1	<1	2	-	-	-	<1
Pemphigus/pemphigoid	<1	✔	<1	-	<1	-	-	<1	-	<1
Photosensitivity	<1	✔	<1	<1	<1	<1	-	<1	-	-
Pruritus	<1	2	<1	<1	-	<1	<1	<1	<1	<1
Rash	<1	4 to 7	<1	<1	<1	2	2	1	<1	<1
Stevens-Johnson syndrome	<1	✔	<1	-	✔	-	-	-	<1	-
Toxic epidermal necrolysis	-	-	<1	-	✔	-	-	-	<1	-

Adverse Events	Benazepril	Captopril	Enalapril	Fosinopril	Lisinopril	Moexipril	Perindopril	Quinapril	Ramipril	Trandolapril
Urticaria	-	-	<1	<1	<1	<1	-	<1	<1	-
Gastrointestinal										
Abdominal pain	-	-	2	<1	2	<1	3	1	<1	<1
Anorexia	-	-	<1	-	-	-	-	-	<1	-
Constipation	<1	-	<1	<1	<1	<1	<1	<1	<1	<1
Diarrhea	-	-	1 to 2	>1	3 to 4	3	4	2	≤1	<1
Dry mouth	-	-	<1	<1	<1	<1	<1	<1	<1	-
Dysgeusia	-	2 to 4	-	-	-	-	-	-	-	-
Dyspepsia	-	✔	<1	-	<1	>1	<1	<1	<1	<6
Hepatitis	-	✔	<1	<1	<1	<1	-	<1	<1	-
Nausea	1	-	1	1 to 2	2	>1	2	2	2	-
Pancreatitis	<1	✔	<1	<1	<1	<1	✔	<1	<1	<1
Vomiting	<1	-	1	1 to 2	<1	<1	2	2	2	<1
Genitourinary										
Decreased libido	<1	-	-	<1	<1	-	-	-	-	<1
Impotence	<1	✔	<1	-	1	-	-	<1	<1	<1
Oliguria	-	<1	<1	-	<1	<1	-	-	-	-
Urinary tract infection	<1	-	1	-	<1	-	3	<1	-	-
Musculoskeletal										
Arthralgia	<1	✔	✔	<1	<1	<1	<1	<1	<1	-
Arthritis	<1	-	✔	✔	<1	-	1	-	<1	-
Muscle cramps	-	-	<1	<1	<1	-	-	-	-	<1
Myalgia	<1	✔	✔	<1	<1	1	<1	-	<1	5
Respiratory										
Asthma	<1	✔	<1	-	<1	-	-	-	-	-
Bronchitis	<1	-	1	-	<1	-	<1	-	-	-
Bronchospasm	-	✔	<1	<1	<1	<1	-	2 to 4	-	-
Cough	1	<2	1 to 2	2 to 10	1 to 4	6	6 to 12	2 to 4	8	2 to 35
Dyspnea	<1	-	1	≥1	<1	<1	<1	-	<1	<1
Pharyngitis	-	-	-	<1	<1	2	3	<1	-	-
Rhinitis	-	✔	-	<1	<1	>1	5	-	-	-
Sinusitis	<1	-	-	<1	<1	>1	<5	-	-	-
Upper respiratory tract infection	-	-	<1	2	2	>1	7	-	✔	<1
Miscellaneous										
Anemia	✔	<1	-	✔	<1	<1	-	<1	<1	-
Angioedema	<1	<1	✔	<1	<1	<1	<1	<1	<1	<1
Asthenia	<1	✔	1 to 2	-	1	-	8	-	2	3
Blurred vision	-	✔	<1	-	<1	-	-	-	-	-
Eosinophilia	-	✔	✔	✔	<1	-	-	-	<1	-
Fever	-	✔	<1	<1	<1	-	<1	-	<1	-
Syncope	<1	✔	1 to 2	<1	<2	<1	<1	<1	<2	6
Tinnitus	-	-	<1	<1	<1	<1	2	-	<1	-
Vasculitis	-	✔	✔	-	<1	-	✔	-	<1	-

✔ Percent not specified
- Event not reported

Table 8. Adverse Drug Events (%) Reported with the Angiotensin-Converting Enzyme Inhibitors-Combination Products[3-18]

Adverse Event	Benazepril and HCTZ	Captopril and HCTZ	Enalapril and HCTZ	Fosinopril and HCTZ	Lisinopril and HCTZ	Quinapril and HCTZ
Cardiovascular						
Angina	-	0.2 to 0.3	-	-	-	-
Cardiac arrest	-	✔	-	-	-	-
Cerebrovascular accident	-	✔	-	-	-	-
Chest pain	-	1	-	0.5 to <2.0	-	1
Hypotension	0.6	✔	-	-	1.4	-
Myocardial infarction	-	0.2 to 0.3	-	-	-	-
Orthostatic hypotension	0.3 to 3.5	✔	2.3	1.8	0.5	≥0.5 to <1.0
Palpitations	-	1	0.5 to 2.0	-	-	≥0.5 to <1.0
Tachycardia	-	1	-	-	-	-
Central Nervous System						
Depression	-	✔	-	-	-	-
Dizziness	6.3	-	8.6	3.2	7.5	4.8
Fatigue	5.2	-	3.9	3.9	3.7	2.9
Headache	3.1	-	5.5	7	5.2	6.7
Insomnia	✔	-	0.5 to 2.0	-	-	1.2
Somnolence/drowsiness	1.2	✔	-	-	-	1.2
Dermatologic						
Flushing	0.3 to 1.0	0.2 to 0.5	✔	0.5 to <2.0	-	-
Pruritus	-	2	-	-	-	✔
Rash	-	4 to 7	✔	0.5 to <2.0	1.2	-
Stevens-Johnson syndrome	✔	✔	✔	✔	-	✔
Gastrointestinal						
Abdominal pain	-	-	-	-	-	1.7
Diarrhea	0.3 to 1.0	✔	2.1	0.5 to <2.0	2.5	1.4
Dysgeusia	-	2 to 4	-	-	-	-
Dyspepsia	-	✔	-	-	-	-
Hepatitis	-	✔	-	-	-	-
Jaundice	✔	✔	✔	✔	-	✔
Nausea	1.4	-	2.5	✔	2.2	✔
Pancreatitis	-	✔	-	-	-	-
Genitourinary						
Decreased libido	-	✔	-	✔	-	-
Impotence	1.2		2.2	-	1.2	≥0.5 to <1.0
Oliguria	-	0.1 to 0.2	-	-	-	-
Musculoskeletal						
Hypertonia	1.5	-	-	-	-	-
Muscle cramps	-	-	2.7	-	2	-
Musculoskeletal pain	-	-	-	2	-	-
Myalgia	-	✔	-	-	-	2.4
Respiratory						
Bronchitis	-	-	-	-	-	1.2
Cough	2.1	0.5 to 2.0	3.5	5.6	3.9	3.2
Rhinitis	-	✔	-	-	-	2
Upper respiratory tract infection	-	-	-	2.3	2.2	1.3

Adverse Event	Benazepril and HCTZ	Captopril and HCTZ	Enalapril and HCTZ	Fosinopril and HCTZ	Lisinopril and HCTZ	Quinapril and HCTZ
Miscellaneous						
Anemia	-	≤0.2	-	-	-	-
Angioedema	0.3	0.1	0.5 to 2.0	0.5 to <2.0	0.3 to 1.0	0.1
Asthenia	-	✔	2.4	-	1.8	≥0.5 to <1.0
Blurred vision	-	✔	-	-	-	-
Eosinophilia	-	✔	-	-	-	-
Fever	-	✔	-	-	-	-
Neutropenia	-	✔	-	0.5 to <2.0	-	-
Syncope	-	✔	-	-	-	-
Viral infection	-	-	-	-	-	1.9

HCTZ=hydrochlorothiazide
✔ Percent not specified
- Event not reported

Table 9. Boxed Warning for the Angiotensin-Converting Enzyme Inhibitors[17]

WARNING
When pregnancy is detected, discontinue therapy as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.

VII. Dosing and Administration

The usual dosing regimens for the angiotensin-converting enzyme inhibitors are listed in Table 10.

Table 10. Usual Dosing Regimens for the Angiotensin-Converting Enzyme Inhibitors[3-18]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Benazepril	Hypertension: Tablet: initial, 5 to 10 mg once daily (for patients not receiving diuretics); maintenance, 20 to 40 mg/day as a single dose or in two equally divided doses; maximum, >80 mg/day has not been evaluated	Hypertension for children ≥6 years of age: Tablet: initial, 0.2 mg/kg once daily; maximum, >0.6 mg/kg (or in excess of 40 mg daily) has not been studied Safety and efficacy in children <6 years of age have not been established.	Tablet: 5 mg 10 mg 20 mg 40 mg
Captopril	Diabetic nephropathy: Tablet: maintenance, 25 mg three times daily Heart failure: Tablet: initial, 25 mg three times daily; maximum, 450 mg/day Hypertension: Tablet: initial, 25 mg two to three times daily; maintenance, after one to two weeks can increase to 50 mg two to three times daily; maximum: 450 mg/day Myocardial infarction (left ventricular dysfunction after myocardial infarction): Tablet: initial, 6.25 mg once, followed by 12.5 mg three times daily; target maintenance, 50 mg three times daily	Safety and efficacy in children have not been established.	Tablet: 12.5 mg 25 mg 50 mg 100 mg
Enalapril	Heart failure: Solution, tablet: initial, 2.5 mg/day; maintenance, 2.5 to 20 mg two times daily; maximum, 40 mg/day in divided doses Hypertension: Solution, tablet: initial, 5 mg once daily; maintenance, 10 to 40 mg/day as a single dose or in two divided doses	Hypertension in children 1 month to 16 years of age: Solution, tablet: initial, 0.08 mg/kg (up to 5 mg) once daily; maximum, >0.58 mg/kg (or in excess of 40 mg) has not been studied Safety and efficacy in children <1 month have not been established.	Solution: 1 mg/mL Tablet: 2.5 mg 5 mg 10 mg 20 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Left ventricular dysfunction: Solution ,tablet: initial, 2.5 mg two times daily; target maintenance, 10 mg/day in divided doses		
Fosinopril	Heart failure: Tablet: initial, 10 mg once daily; maintenance, 20 to 40 mg/day; maximum, 40 mg once daily Hypertension: Tablet: initial, 10 mg once daily; maintenance, 20 to 40 mg/day in a single or divided dose(s); maximum, 80 mg/day	Hypertension in children 6 to 16 years of age: Tablet (>50 kg): 5 to 10 mg once daily Safety and efficacy in children <6 years of age have not been established.	Tablet: 10 mg 20 mg 40 mg
Lisinopril	Heart failure: Solution, tablet: initial, 5 mg once daily; maintenance, 5 to 20 mg once daily Hypertension: Solution, tablet: initial, 10 mg once daily; maintenance, 20 to 40 mg once daily Post-myocardial infarction: Solution, tablet: initial, 5 mg every 24 hours for two doses, followed by 10 mg every day for 6 weeks	Hypertension in children 6 to 16 years of age: Solution, tablet: initial, 0.07 mg/kg (up to 5 mg) once daily; doses >0.6 mg/kg (or in excess of 40 mg) have not been studied Safety and efficacy in children <6 years of age have not been established.	Solution: 1 mg/ mL Tablet: 2.5 mg 5 mg 10 mg 20 mg 30 mg 40 mg
Moexipril	Hypertension: Tablet: initial, 7.5 mg once daily; maintenance, 7.5 to 30 mg/day in a single or divided dose(s); maximum, 60 mg/day	Safety and efficacy in children have not been established.	Tablet: 7.5 mg 15 mg
Perindopril	Cardiovascular risk reduction (coronary artery disease): Tablet: initial: 4 mg once daily for 2 weeks; maintenance, increase as tolerated to 8 mg once daily Hypertension: Tablet: initial, 4 mg once daily; maintenance, 4 to 8 mg/day in a single or divided dose(s); maximum, 16 mg/day	Safety and efficacy in children have not been established.	Tablet: 2 mg 4 mg 8 mg
Quinapril	Heart failure: Tablet: initial, 5 mg twice daily; maintenance, titrate at weekly intervals to 10 to 20 mg two times daily Hypertension: Tablet: initial, 10 to 20 mg once daily; maintenance, 20 to 80 mg/day in a single or divided dose(s)	Safety and efficacy in children have not been established.	Tablet: 5 mg 10 mg 20 mg 40 mg
Ramipril	Cardiovascular risk reduction:	Safety and efficacy in	Capsule:

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Capsule: initial, 2.5 mg once daily for one week, followed by 5 mg once daily for three weeks; maintenance, 10 mg once daily Hypertension: Capsule: initial, 2.5 mg once daily; maintenance, 2.5 to 20 mg/day in single or divided dose(s) Post-myocardial infarction (heart failure after myocardial infarction): Capsule: initial, 2.5 mg twice daily; target maintenance, 5 mg twice daily	children have not been established.	1.25 mg 2.5 mg 5 mg 10 mg
Trandolapril	Post-myocardial infarction (left ventricular dysfunction or heart failure after myocardial infarction): Tablet: initial, 1 mg once daily; maintenance, titrate as tolerated to target of 4 mg once daily Hypertension: Tablet: initial, 1 mg once daily in non-African American patients and 2 mg once daily in African American patients; maintenance, 2 to 4 mg once daily	Safety and efficacy in children have not been established.	Tablet: 1 mg 2 mg 4 mg
Combination Products			
Benazepril and HCTZ	Hypertension: Tablet: initial, 10-12.5 or 20-12.5 mg/day if not adequately controlled on benazepril monotherapy; maintenance, titrate dose by clinical effect	Safety and efficacy in children have not been established.	Tablet: 5-6.25 mg 10-12.5 mg 20-12.5 mg 20-25 mg
Captopril and HCTZ	Hypertension: Tablet: initial, 25-5 mg once daily; titrate dose by clinical effect; maximum, 150-50 mg/day	Safety and efficacy in children have not been established.	Tablet: 25-15 mg 25-25 mg 50-15 mg 50-25 mg
Enalapril and HCTZ	Hypertension: Tablet: maximum, four tablets of 5-12.5 mg or two tablets of 10-25 mg	Safety and efficacy in children have not been established.	Tablet: 5-12.5 mg 10-25 mg
Fosinopril and HCTZ	Hypertension: Tablet: titrate dose by clinical effect	Safety and efficacy in children have not been established.	Tablet: 10-12.5 mg 20-12.5 mg
Lisinopril and HCTZ	Hypertension: Tablet: initial, 10-12.5 or 20-12.5 mg/day after failure on monotherapy; titrate dose by clinical effect; maximum, 80-50 mg/day	Safety and efficacy in children have not been established.	Tablet: 10-12.5 mg 20-12.5 mg 20-25 mg
Quinapril and HCTZ	Hypertension: Tablet: initial, 10-12.5 or 20-12.5 mg/day; maintenance, titrate dose by clinical effect	Safety and efficacy in children have not been established.	Tablet: 10-12.5 mg 20-12.5 mg 20-25 mg

HCTZ=hydrochlorothiazide

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the angiotensin-converting enzyme inhibitors are summarized in Table 11.

Table 11. Comparative Clinical Trials with the Angiotensin-Converting Enzyme Inhibitors

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cardiovascular Disease				
Jamerson et al.[38] (2008) ACCOMPLISH Benazepril 20 to 40 mg QD and HCTZ 12.5 to 25 mg QD vs benazepril 20 to 40 mg QD and amlodipine 5 to 10 mg QD	AC, DB, MC, RCT Patients >60 years of age with HTN and at high risk of cardiovascular events	N=11,506 36 months (mean)	Primary: The composite of death from cardiovascular causes, nonfatal MI, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and coronary revascularization. Secondary: Death from cardiovascular causes, nonfatal MI, and nonfatal stroke	Primary: There were 552 primary-outcome events in the benazepril plus amlodipine group (9.6%) and 679 events in the benazepril plus HCTZ group (11.8%). The absolute risk reduction with benazepril plus amlodipine therapy was 2.2% and the relative risk reduction was 19.6% compared to benazepril plus HCTZ (HR, 0.80; 95% CI, 0.72 to 0.90; P<0.001). Secondary: For the secondary end point of death from cardiovascular causes, nonfatal MI, and nonfatal stroke, there were 288 (5%) events in the benazepril plus amlodipine group compared to 364 (6.3%) events in the benazepril plus HCTZ group. The absolute risk reduction with benazepril plus amlodipine therapy was 1.3% and the RR reduction was 21.2% compared to benazepril plus HCTZ (HR, 0.79; 95% CI, 0.67 to 0.92; P=0.002).
Weber et al.[39] (2010) ACCOMPLISH Benazepril and amlodipine 40-5 to 40-10 mg/day, followed by forced titration after 1 month on	Prespecified subanalysis of ACCOMPISH Men and women >60 years of age with HTN and at high risk for cardiovascular events (history of	N=6,946 Mean treatment duration 29.7 months for benazepril and amlodipine group and 29.5 months for	Primary: Primary: Time to first event (composite of cardiovascular event and death from cardiovascular causes)	Primary: The primary endpoint occurred in 8.8% of diabetic patients in the benazepril and amlodipine group and 11.0% in the benazepril and HCTZ group (HR, 0.79; P=0.003; NNT, 46). In high risk diabetic patients, 13.6% of patients in the benazepril and amlodipine group and 17.3% in the benazepril and HCTZ group (HR, 0.77, P=0.007; NNT, 28). Secondary: Due to early termination, the study had limited power to detect differences in the diabetic subgroups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
benazepril and amlodipine 20-5 mg (fixed-dose combination product) vs benazepril and HCTZ 40-12.5 to 40-25 mg/day, followed by forced titration after one month on benazepril and HCTZ 20-12.5 mg (fixed-dose combination product)	coronary events, MI, revascularization, or stroke; impaired renal function; peripheral arterial disease, left ventricular hypertrophy; or diabetes) (Subanalysis of patients with diabetes)	benazepril and HCTZ group	Secondary: Composite of cardiovascular events (the primary endpoint excluding fatal events) and composite of death from cardiovascular disease, nonfatal stroke and nonfatal MI	Peripheral edema was higher in the benazepril and amlodipine group compared to the benazepril and HCTZ group.
Weber et al.[40] (2013) ACCOMPLISH Benazepril and amlodipine 40-5 to 40-10 mg/day, followed by forced titration after 1 month on benazepril and amlodipine 20-5 mg (fixed-dose combination product) vs	Subanalysis of ACCOMPLISH based on body size Patients >60 years of age with HTN and at high risk of cardiovascular events	N=11,482 Duration not specified	Primary: Composite of cardiovascular death or nonfatal MI or stroke Secondary: Cardiovascular death, total MI, total stroke	Primary: In patients receiving benazepril and HCTZ, the primary endpoint (per 1,000 patient-years) was 30.7 in normal weight (BMI <25), 21.9 in overweight (BMI ≥25 to <30), and 18.2 in obese patients (BMI ≥30) (overall P=0.0034). In patients receiving benazepril and amlodipine, the primary endpoint did not differ between the three BMI groups (18.2, 16.9, and 16.5, respectively; P=0.9721). In obese patients, primary event rates were similar between the two treatments, but rates were significantly lower with benazepril and amlodipine in overweight patients (HR, 0.76; 95% CI, 0.59 to 0.94; P=0.0369) and normal weight patients (HR, 0.57; 95% CI, 0.39 to 0.84; P=0.0037). Secondary: Comparing obese and overweight patients, event rates were all numerically lower, but not significantly lower, in obese patients. Cardiovascular deaths were significantly lower in overweight patients compared to normal weight patients (HR, 57; 95% CI, 0.37 to 0.89; P=0.0125). Cardiovascular death (HR, 0.40; 95% CI, 0.25 to 0.63;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
benazepril and HCTZ 40-12.5 to 40-25 mg/day, followed by forced titration after 1 month on benazepril and HCTZ 20-12.5 mg (fixed-dose combination product)				P<0.0001) and total stroke (HR, 0.60; 95% CI, 0.37 to 0.96; P=0.0335) were significantly lower in obese patients compared to normal weight patients.
Swedberg et al.[41] (1992) CONSENSUS II Enalapril 5 to 20 mg/day vs placebo Treatment was started with an IV infusion of 1 mg of enalaprilat administered over 3 hours followed by oral enalapril 6 hours after the infusion was stopped.	DB, MC, PC, PG, RCT Patients who presented within 24 hours of the onset of acute MI symptoms	N=6,090 180 days	Primary: Mortality rates within 6 months Secondary: Mortality within 1 month, cause of death, re-infarction, or worsening heart failure	Primary: Mortality rates according to life-table analysis between the enalapril and placebo groups at six months were not significantly different (11 vs 10.2%; P=0.26). The RR associated with enalapril treatment and based on the mortality curves was 1.10 (95% CI, 0.93 to 1.29). Secondary: Mortality rates between the enalapril and placebo groups at one month were not significantly different (7.2 vs 6.3%; P=0.26). Death due to progressive heart failure occurred more frequently in patients treated with enalapril than placebo (4.3 vs 3.4%; P=0.06). There were no significant differences in the rate of reinfarction between the enalapril or placebo groups (P value not significant). Change in therapy because of heart failure occurred more in the placebo group (P<0.006) but there were no significant differences in hospitalization for heart failure (P value not significant). Note: The first CONSENSUS trial excluded patients with a recent MI or unstable angina. The study was stopped early after recruiting 6,090 of the intended 9,000 patients since more patients had died on the drug than on placebo (although the difference was not statistically significant).
Wing et al.[42] (2003)	MC, OL, PRO, RCT	N=6,083	Primary: All cardiovascular	Primary: By the end of the study, blood pressure had decreased to a similar extent in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ANBP2 Enalapril vs HCTZ The choice of the specific agent and dose was made by the family practitioner.	Patients 65 to 84 years of age with average SBP while sitting of ≥160 mm Hg or an average DBP of ≥90 mm Hg (if the SBP was ≥140 mm Hg)	4.1 years (median)	events or death from any cause (both initial and subsequent fatal and nonfatal cardiovascular events) Secondary: Not reported	both groups (a decrease of 26/12 mm Hg). There were 695 cardiovascular events or deaths from any cause in the ACE inhibitor group (56.1 per 1,000 patient-years; HR, 0.89; 95% CI, 0.79 to 10; P=0.05) compared to 736 in the diuretic group (59.8 per 1,000 patient-years). The beneficial effects of ACE inhibitor treatment were more evident in male subjects (HR, 0.83; 95% CI, 0.71 to 0.97; P=0.02). The rates of nonfatal cardiovascular events and MI decreased with ACE inhibitor treatment, whereas a similar number of strokes occurred in each group (although there were more fatal strokes in the ACE inhibitor group). Secondary: Not reported
Nissen et al.[43] (2004) CAMELOT Enalapril 10 to 20 mg/day vs amlodipine 5 to 10 mg/day vs placebo	DB, MC, PC, RCT Patients 30 to 79 years of age requiring coronary angiography for evaluation for chest pain or PCI and a diastolic pressure <100 mm Hg, with or without treatment	N=1,991 2 years	Primary: Composite of cardiovascular events (cardiovascular death, nonfatal MI, resuscitated cardiac arrest, coronary revascularization, hospitalization for angina pectoris, hospitalization for CHF, fatal or nonfatal stroke or TIA, and any new diagnosis of PVD), nominal change in percent atheroma volume (substudy)	Primary: Cardiovascular events occurred in 23.1% of placebo-treated patients, 16.6% amlodipine-treated patients (HR, 0.69; 95% CI, 0.54 to 0.88; P=0.003) and 20.2% enalapril-treated patients (HR, 0.85; 95% CI, 0.67 to 17; P=0.16). The primary end point comparison for enalapril vs amlodipine was not significant (HR, 0.81; 95% CI, 0.63 to 14; P=0.10). Secondary: Coronary revascularization was reduced in the amlodipine group from 15.7 to 11.8% (HR, 0.73; 95% CI, 0.54 to 0.98; P=0.03). Hospitalization for angina was reduced in the amlodipine group from 12.8 to 7.7% (HR, 0.58; 95% CI, 0.41 to 0.82; P=0.002). Individual components of the primary end point generally showed fewer events with enalapril treatment vs placebo, but none of the comparisons reached statistical significance. For components of the primary end point, only the rate of hospitalization for angina showed a statistically significant difference between amlodipine

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Incidence of adverse events; all-cause mortality, incidence of revascularization in vessels that had undergone previous stent placement	and enalapril (HR, 0.59; 95% CI, 0.42 to 0.84; P=0.003). A trend toward fewer episodes of revascularization in patients undergoing intervention at baseline was observed for amlodipine vs enalapril (HR, 0.66; 95% CI, 0.40 to 16; P=0.09). The mean change in percent atheroma volume was 0.5% for amlodipine (P=0.12 vs placebo), 0.8% for enalapril (P=0.32 vs placebo) and 1.3% for placebo. In patients with SBP greater than the mean, the amlodipine group showed a significantly slower progression (0.2%) compared to placebo (2.3%; P=0.02). Compared to baseline, intravascular ultrasound showed progression in patients receiving placebo (P<0.001), a trend toward progression with enalapril (P=0.08) and no progression in patients receiving amlodipine (P=0.31). For the amlodipine group, correlation between blood pressure reduction and progression was r=0.19 (P=0.07). Discontinuation from the study for treatment-emergent adverse events was low, averaging 0.4% and not statistically significant between the three treatment groups. The only statistically significant difference in secondary end points was that amlodipine demonstrated a significant reduction in revascularization after previous stent placement compared to placebo (4.1 vs 7.9%; HR, 0.49; 95% CI, 0.31 to 0.78; P=0.002). The rate of revascularization was lower than enalapril (6.2%) but not statistically significant (HR 0.66, 95% CI, 0.40 to 16; P=0.09).
Pitt et al.[44] (2003) 4E-Left Ventricular Hypertrophy Study Enalapril 40 mg QD vs	AC, DB, PG, RCT Patients with left ventricular hypertrophy, a history of HTN and predominantly in sinus rhythm	N=153 9 months	Primary: Change in left ventricular mass as assessed by MRI Secondary: Reduction in SBP and DBP, response rate (DBP <90 mm Hg), change in urine albumin creatinine ratio	Primary: Both treatments were associated with a significant reduction in left ventricular mass from baseline (P<0.001). The difference in left ventricular mass reduction from baseline between the two treatments was not significant (P=0.258). While enalapril plus eplerenone therapy demonstrated a significantly greater reduction in left ventricular mass from baseline compared to eplerenone therapy (P=0.007); the effect was not statistically different from that observed with enalapril therapy (P=0.107). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
eplerenone 200 mg QD vs enalapril 10 mg plus eplerenone 200 mg If the blood pressure was uncontrolled on study medication at week 8, OL HCTZ 12.5 to 25 mg/day and/or amlodipine 10 mg/day were allowed.				The SBP was reduced significantly more in enalapril plus eplerenone-treated patients compared to eplerenone-treated patients (P=0.048). The other treatment groups exhibited statistically comparable reductions from baseline in mean SBP and DBP (P value not reported). While 70.0% of eplerenone-treated patients responded to therapy, 40.7% of enalapril-treated patients responded (P=0.003). In addition, 79.6% of enalapril plus eplerenone-treated patients responded to therapy compared to 40.7% enalapril-treated patients (P=0.001). Enalapril plus eplerenone therapy was associated with a significant reduction in urine albumin creatinine ratio compared to either eplerenone or enalapril therapy (P<0.05). Adverse events were reported with similar incidence among all treatment groups (P value not reported). Cough was significant in enalapril-treated patients compared to eplerenone-treated patients (P=0.033). Two cases of gynecomastia were reported (one eplerenone- and one enalapril plus eplerenone-treated patients). Four patients (three enalapril- and one enalapril plus eplerenone-treated patients) experienced impotence during the trial. Seven eplerenone-, two enalapril- and three enalapril plus eplerenone-treated patients experienced serious hyperkalemia (≥6.0 mmol/L).
Hansson et al.[45] (1999) STOP-Hypertension Enalapril 10 mg or lisinopril 10 mg QD vs felodipine 2.5 mg or isradipine 2.5 mg QD	MC, OL, PRO, RCT Men and women, age 70 to 84 years with HTN (SBP ≥180mm Hg or DBP ≥105 mm Hg or both)	N=6,614 4 years	Primary: Fatal stroke, fatal MI, other fatal cardiovascular events Secondary: Blood pressure	Primary: The rate of prevention of cardiovascular deaths was similar in all groups (RR, 0.97 to 14; 95% CI, 0.86 to 1.26). Fatal cardiovascular events, including fatal stroke and fatal myocardial infarction MI, occurred in 19.8 per 1,000 patient-years in the β-blocker and/or HCTZ group, in the felodipine or isradipine group and in the enalapril or lisinopril group (RR, 0.99; 95% CI, 0.84 to 1.16). The RR of cardiovascular death in patients in the enalapril or lisinopril group as compared to the felodipine or isradipine group was 14 (95% CI, 0.86 to 1.26; P=0.67.) Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs atenolol 50 mg or metoprolol 100 mg or pindolol 5 mg QD and/or HCTZ 25 mg with amiloride 2 to 5 mg QD				Decreases in blood pressure were similar among the groups.
ALLHAT[46] (2002) ALLHAT Lisinopril 10 to 40 mg/day vs amlodipine 2.5 to 10 mg/day vs chlorthalidone 12.5 to 25 mg/day Doses were titrated to achieve a goal blood pressure of <140/90 mm Hg.	DB, MC, RCT Patients ≥55 years with HTN and ≥1 additional CHD risk factor	N=33,357 4.9 years (mean)	Primary: Combined fatal CHD or nonfatal MI Secondary: All-cause mortality, fatal and nonfatal stroke, combined CHD, combined cardiovascular disease (combined CHD, stroke, treated angina without hospitalization, heart failure, and PAD)	Primary: There were no significant differences in the primary outcome between lisinopril (11.4%), amlodipine (11.3%), and chlorthalidone (11.5%). Secondary: All-cause mortality did not differ between groups. Five year SBPs were significantly higher in the lisinopril (2 mm Hg; P<0.001) and amlodipine groups (0.8 mm Hg; P=0.03) compared to chlorthalidone, and five year DBPs were significantly lower with amlodipine (0.8 mm Hg; P<0.001). Amlodipine had a higher six year rate of heart failure compared to chlorthalidone (10.2 vs 7.7%; RR, 1.38; 95% CI, 1.25 to 1.52). Lisinopril had a higher six year rate of combined cardiovascular disease (33.3 vs 30.9%; RR, 1.10; 95% CI, 15 to 1.16); stroke (6.3 vs 5.6%; RR, 1.15; 95% CI, 12 to 1.30) and heart failure (8.7 vs 7.7%; RR, 1.19; 95% CI, 17 to 1.31).
Black et al.[47] (2008) ALLHAT Amlodipine 2.5 to	MC, RCT Men and women, age 55 years old and older, with HTN and	N=17,515 4.9 years (mean)	Primary: Fatal coronary heart disease and nonfatal MI	Primary: For patients with metabolic syndrome, there was no significant difference in rates of coronary heart disease and nonfatal MI with amlodipine vs chlorthalidone (RR, 0.96; 95% CI, 0.79 to 1.16), or lisinopril vs chlorthalidone (RR, 15; 95% CI, 0.88 to 1.27).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
10 mg QD vs lisinopril 10 to 40 mg QD vs chlorthalidone 12.5 to 25 mg QD	metabolic syndrome		Secondary: All cause mortality, fatal and nonfatal stroke, combined coronary heart disease, combined cardiovascular disease	Secondary: For patients with metabolic syndrome, there were no significant differences found between amlodipine vs chlorthalidone in all secondary endpoints (P value not significant). For patients without metabolic syndrome, amlodipine treatment was associated with significantly more heart failure, but in patients with metabolic syndrome, there was no difference (P=0.03). Patients with metabolic syndrome who received lisinopril experienced more heart failure and cardiovascular disease than those who received chlorthalidone (RR, 1.31; 95% CI, 14 to 1.64 and RR, 1.19; 95% CI, 17 to 1.32).
Rahman et al.[48] (2012) ALLHAT Lisinopril 10 to 40 mg/day vs amlodipine 2.5 to 10 mg/day vs chlorthalidone 12.5 to 25 mg/day	Long-term, post-trial, follow-up Patients in ALLHAT stratified based on eGFR	N=31,350 4 to 8 years	Primary: Cardiovascular mortality Secondary: Total mortality, CHD, cardiovascular disease, stroke, heart failure, ESRD	Primary: After an average of 8.8 years of follow-up, total mortality was significantly higher in patients with moderate/severe eGFR reduction (eGFR <60 mL/min/1.73 m^2) compared to patients with normal/increased (eGFR ≥90 mL/min/1.73 m^2) and mildly reduced eGFR (eGFR 60 to 89 mL/min/1.73 m^2) (P<0.001). In patients with moderate/severe eGFR reduction, there was no significant difference in cardiovascular mortality between chlorthalidone and amlodipine (P=0.64), or chlorthalidone and lisinopril (P=0.56). Secondary: No significant differences were observed for any of the secondary endpoints among eGFR reduction groups.
Muntner et al.[49] (2014) ALLHAT Chlorthalidone 12.5 to 25 mg/day	Post-hoc analysis of ALLHAT Patients in ALLHAT with 5, 6, or 7 visits in 6 to 28 months of follow-up	N=24,004 6 to 28 months	Primary: Visit-to-visit variability (VVV) of blood pressure Secondary: Not reported	Primary: Each measure of VVV of SBP was lower among participants randomized to chlorthalidone and amlodipine compared with those randomized to lisinopril. All four VVV of SBP metrics were lower among participants randomized to amlodipine vs chlorthalidone after full multivariable adjustment.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs amlodipine 2.5 to 10 mg/day vs lisinopril 10 to 40 mg/day				After multivariable adjustment including mean SBP across visits and compared with participants randomized to chlorthalidone, participants randomized to amlodipine had a 0.36 (standard error [SE]: 0.07) lower standard deviation (SD) of SBP and participants randomized to lisinopril had a 0.77 (SE=0.08) higher SD of SBP. Results were consistent using other VVV of SBP metrics. These data suggest chlorthalidone and amlodipine are associated with lower VVV of SBP than lisinopril. Secondary: Not reported
Bangalore et al.[50] (2017) ALLHAT Lisinopril 10 to 40 mg/day vs amlodipine 2.5 to 10 mg/day vs chlorthalidone 12.5 to 25 mg/day	Post-hoc analysis of ALLHAT Patients in ALLHAT with average blood pressure ≥140 mmHg systolic or ≥90 mm Hg diastolic on ≥3 antihypertensive medications, or blood pressure <140/90 mmHg on ≥4 antihypertensive medications (i.e., identified as having apparent treatment-resistant hypertension) at 2-year follow up	N=14,684 4.9 years (mean)	Primary: Combined fatal CHD or nonfatal MI Secondary: All-cause mortality, fatal and nonfatal stroke, combined CHD, combined cardiovascular disease (combined CHD, stroke, treated angina without hospitalization, heart failure, and PAD)	Primary: Of participants assigned to chlorthalidone, amlodipine, or lisinopril, 9.6%, 11.4%, and 19.7%, respectively, had treatment-resistant hypertension. During mean follow-up of 2.9 years, primary outcome incidence was similar for those assigned to chlorthalidone compared with amlodipine or lisinopril (amlodipine- vs chlorthalidone-adjusted HR, 0.86; 95% CI, 0.53 to 1.39; P=0.53; lisinopril- vs chlorthalidone-adjusted HR, 1.06; 95% CI, 0.70 to 1.60; P=0.78). Secondary: Secondary outcome risks were similar for most comparisons except coronary revascularization, which was higher with amlodipine than with chlorthalidone (HR, 1.86; 95% CI, 1.11 to 3.11; P=0.02). An as-treated analysis based on diuretic use produced similar results.
Fox et al.[51] (2003) EUROPA Perindopril 8 mg QD	DB, MC, PC, RCT Patients ≥18 years of age with evidence of CHD (e.g., MI >3 months before screening,	N=12,218 4.2 years (mean)	Primary: Composite of cardiovascular death, MI, or cardiac arrest Secondary:	Primary: Patients treated with perindopril had a significant reduction in the primary outcome compared to patients treated with placebo (8 vs 10%; RR reduction, 20%; 95% CI, 9 to 29; P=0.0003). The benefit began to appear at one year and gradually increased throughout the trial. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	percutaneous or surgical coronary revascularization >6 months before screening, 70% narrowing of 1 or more major coronary arteries, history of chest pain) and without clinical heart failure or uncontrolled HTN		Composite of total mortality, nonfatal MI, hospital admission for unstable angina, and cardiac arrest with successful resuscitation; cardiovascular mortality and nonfatal MI; individual components of the secondary outcomes and revascularization, stroke, and admission for heart failure	Compared to placebo, treatment with perindopril was associated with reductions in all secondary end points. However, not all changes were significant. There was a 14% reduction in total mortality, nonfatal MI, unstable angina, and cardiac arrest (P=0.0009). There was a 22% reduction in nonfatal MI with perindopril (P=0.001). Total mortality was 11% lower with perindopril but this finding was not significant (P=0.1). Hospital admission for heart failure was significantly reduced with perindopril by 39% (P=0.002).
PREAMI Investigators[52] (2006) Perindopril 8 mg/day vs placebo	DB, MC, PC, PG, RCT Patients ≥65 years with LVEF ≥40% and recent acute MI	N=1,252 12 months	Primary: Composite of death, hospitalization for heart failure or left ventricular remodeling Secondary: Cardiovascular death, hospitalization for reinfarction or angina, revascularization	Primary: The primary end point occurred in 35% of patients taking perindopril and 57% of patients on placebo, with an absolute risk reduction of 0.22 (95% CI, 0.16 to 0.28; P<0.001). A total of 126 patients (28%) and 226 patients (51%) in the perindopril and placebo groups, respectively, experienced remodeling (P<0.001). The mean increase in left ventricular end-diastolic volume was 0.7 mL with perindopril compared to 4.0 mL with placebo (P<0.001). Secondary: Cardiovascular death, hospitalization for subsequent acute MI or angina or revascularization was infrequent and not modified by treatment. Conclusion: Perindopril treatment for one year reduced progressive left ventricular remodeling but was not associated with better clinical outcomes.
ADVANCE	DB, MC, PC, RCT	N=11,140	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Collaborative Group[53] (2007) Perindopril (2 to 4 mg) and indapamide (0.625 to 1.25 mg) QD vs placebo	Adults 55 years of age or older who were diagnosed with type 2 diabetes at age 30 or older, and a history of cardiovascular disease or ≥1 other risk factor for cardiovascular disease	Mean 4.3 years	Composites of major macrovascular and microvascular events (death from cardiovascular disease, nonfatal stroke, nonfatal MI, or new renal or diabetic eye disease) Secondary: Macrovascular and microvascular endpoints analyzed separately	The relative risk of a major macrovascular or microvascular event was reduced by 9% (861 [15.5%] active vs 938 [16.8%] placebo; HR, 0.91, 95% CI 0.83 to 10, P=0.04). Secondary: The RR of death from cardiovascular disease was reduced by 18% (211 [3.8%] active vs 257 [4.6%] placebo; 0.82, 0.68-0.98, p=0.03) and death from any cause was reduced by 14% (408 [7.3%] active vs 471 [8.5%] placebo; 0.86, 0.75-0.98, P=0.03).
HOPE Investigators[54] (2000) Ramipril 10 mg QD vs placebo	DB, RCT, two-by-two factorial trial Men and women ≥55 years old with history of CAD, stroke, PVD, or diabetes and ≥1 other cardiovascular risk factor and who were not known to have a low ejection fraction (<40%) or heart failure	N=9,297 5 years (mean)	Primary: Composite of death from cardiovascular causes, MI, or stroke and each outcome separately Secondary: Death from any cause, revascularization, hospitalization for unstable angina or heart failure, and complications related to diabetes Other end points: Worsening angina,	Primary: Fewer patients on ramipril than placebo (14.0 vs 17.8%, respectively) died of cardiovascular causes or had a MI or stroke (RR, 0.78; 95% CI, 0.70 to 0.86; P<0.001). Treatment with ramipril reduced the rates of death from cardiovascular causes (RR, 0.74; P<0.001), MI (RR, 0.80; P<0.001), and stroke (RR, 0.68; P<0.001). Secondary: The risk of death from any cause was also significantly reduced by treatment with ramipril (RR, 0.84; P=0.005). Significantly fewer patients treated with ramipril underwent revascularization compared to placebo (RR, 0.85; P=0.002). Fewer hospitalizations for heart failure were reported with ramipril vs placebo but the risk reduction was not statistically significant (RR, 0.88; P=0.25).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			cardiac arrest, heart failure, unstable angina with ECG changes, and the development of diabetes	Fewer complications related to diabetes were reported in patients receiving ramipril (RR, 0.84; P=0.03). Other end points: Significantly fewer patients treated with ramipril than placebo group had the following: worsening angina (RR, 0.89; P=0.004), cardiac arrest (RR, 0.62; P=0.02), heart failure (RR 0.77; P<0.001), and new diagnosis of diabetes (RR, 0.66; P<0.001). There was no difference between treatment groups for unstable angina with ECG changes (RR, 0.97; P=0.76).
ONTARGET Investigators[55] (2008) Ramipril 10 mg/day vs telmisartan 80 mg/day vs ramipril 10 mg/day and telmisartan 80 mg/day	DB, MC, PC, RCT Patients with coronary, peripheral, or cerebrovascular disease or diabetes with end-organ damage	N=25,620 56 months (median follow-up)	Primary: Death from cardiovascular causes, MI, stroke or hospitalization for heart failure Secondary: Composite of death from cardiovascular causes, MI or stroke; heart failure, worsening or new angina, new diagnosis diabetes mellitus, new atrial fibrillation, renal impairment, revascularization procedures	Primary: The primary outcome occurred in 16.5, 16.7, and 16.3% of patients receiving ramipril, telmisartan and combination therapy, respectively. Secondary: The composite of death from cardiovascular causes, MI or stroke occurred in 14.1% of patients in the ramipril group and 13.9% of patients in the telmisartan group (RR, 0.99; 95% CI, 0.91 to 17; P=0.001 for non-inferiority). Combination therapy was not significantly better than ramipril alone (RR, 0.99; 95% CI, 0.92 to 17). There were no significant differences in the rates of secondary outcomes, except for renal dysfunction, which occurred in 10.2% of patients receiving ramipril, 10.6% of patients receiving telmisartan and 13.5% of patients receiving combination therapy (P<0.001 vs ramipril; P value not reported vs telmisartan). As compared to the ramipril group, the telmisartan group had lower rates of cough (1.1 vs 4.2%; P<0.001) and angioedema (0.1 vs 0.3%; P=0.01) and a higher rate of hypotensive symptoms (2.6 vs 1.7%; P<0.001); the rate of syncope was the same in the two groups (0.2%). As compared to the ramipril group, combination therapy had an increased risk of hypotensive symptoms (4.8 vs 1.7%; P<0.001), syncope (0.3 vs 0.2%; P=0.03) and renal dysfunction (13.5 vs 10.2%; P<0.001).
Redon et al.[56] (2012) ONTARGET	Post-hoc analysis Patients with	N=25,584 56 months	Primary: Composite of cardiovascular	Primary: The primary outcome occurred in 20.2% (n=1,938) and 14.2% (n=2,276) of diabetic and nondiabetic patients. Compared to nondiabetic patients,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ramipril 10 mg/day vs telmisartan 80 mg/day vs ramipril 10 mg/day and telmisartan 80 mg/day	coronary, peripheral, or cerebrovascular disease or diabetes with end-organ damage	(median follow-up)	death, nonfatal MI, nonfatal stroke, and hospitalized heart failure Secondary: Not reported	diabetic patients had a significantly higher risk for the primary endpoint (HR, 1.48; 95% CI, 1.38 to 1.57) and cardiovascular death (HR, 1.56; 95% CI, 1.42 to 1.71), MI (HR, 1.30; 95% CI, 1.17 to 1.46), stroke (HR, 1.39; 95% CI, 1.23 to 1.56), and CHF hospitalization (HR, 2.06; 95% CI, 1.82 to 2.32). Cardiovascular risk was significantly higher in diabetic patients compared to nondiabetic patients regardless of changes in SBP during treatment. In all patients, progressively greater SBP reductions were accompanied by reduced risk for the primary outcome only if baseline SBP levels ranged from 143 to 155 mm Hg; except for stroke, there was no benefit in fatal and nonfatal cardiovascular outcomes by reducing SBP <130 mm Hg. Secondary: Not reported
Mann et al.[57] (2013) ONTARGET Ramipril with telmisartan	Subanalysis Patients in the ONTARGET trial with diabetes mellitus	N=3163 with CKD N=6465 no CKD 56 months	Primary: Composite of death from cardiovascular cause, nonfatal MI, nonfatal stroke or hospitalization for CHF Secondary: composite renal outcome for this analysis was defined posthoc as chronic dialysis (>2 months) or a doubling of baseline serum creatinine	Primary: The stroke rate in all participants with diabetes was not different between the treatment groups, 1.19 and 1.22 per 100 patient-years in those on dual and monotherapy, respectively (HR, 0.99; 95% CI, 0.82 to 1.20). The results were consistent in those with or without renal disease (P value for interaction =0.60; 1.59 vs 1.55 and 1.01 vs 1.08 strokes per 100 patient-years, respectively). Results for other major outcomes indicated no differences and no interaction of renal subgroups with treatment effects. Secondary: Dialysis-dependent acute kidney injury tended to occur more frequently in those allocated to dual than with monotherapy, 0.14 vs 0.08 cases per 100 patient-years, (HR, 1.55; 95% CI, 0.84 to 2.85), and hyperkalemia was more frequent, 1.82 vs 1.07 cases per 100 patient-years (HR, 1.71; 95% CI, 1.44 to 2.02). Both adverse outcomes were more frequent in those with renal disease; however, the excess due to dual therapy was similar in those with and without renal disease.
PEACE Trial Investigators[58]	DB, PC, RCT	N=8,290	Primary: Combined rate of	Primary: No significant differences in the primary outcome measures between

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2004) PEACE Trandolapril 4 mg/day vs placebo	Patients ≥50 years of age with stable CAD and normal or slightly reduced left ventricular function (LVEF >40%)	4.8 years (median)	nonfatal MI, death from cardiovascular causes, or coronary revascularization procedures Secondary: Composite of death from cardiovascular causes, nonfatal MI, revascularization, unstable angina, new CHF, stroke, PVD, and cardiac arrhythmia	trandolapril and placebo were reported (21.9 vs 22.5%; HR, 0.96; 95% CI, 0.88 to 16; P=0.43). Secondary: No significant differences in secondary outcome measures between trandolapril and placebo were reported (P>0.05). Side effects leading to discontinuation of study medication occurred in 14.4% of patients receiving trandolapril and 6.5% of patients receiving placebo (P<0.001). The rates of cough (39.1 vs 27.5%; P<0.01) and syncope (4.8 vs 3.9%; P=0.04) were higher in patients receiving trandolapril vs placebo. Note: This trial was conducted in low-risk patients with stable CAD and normal or slightly reduced left ventricular function. However, the HOPE trial was conducted in patients with coronary or other vascular disease or with diabetes and another cardiovascular risk factor and the EUROPA trial was conducted in patients with evidence of CHD.
Pilote et al.[59] (2004) Captopril (50 mg), enalapril (10 mg), fosinopril (10 mg), lisinopril (10 mg), perindopril (4 mg), quinapril (20 mg), and ramipril (5 mg)	RETRO Patients ≥65 years who were hospitalized for acute myocardial infarction and filled a prescription for an ACE inhibitor within 30 days of discharge and who continued to receive the same drug for ≥1 year	N=7,512 Average of 2.3 years since discharge	Primary: 1-year mortality following an acute MI Secondary: Readmissions due to cardiac complications	Primary: Captopril (HR, 1.56; 95% CI, 1.13 to 2.15), enalapril (HR, 1.47; 95% CI, 1.14 to 1.89), fosinopril (HR, 1.71; 95% CI, 1.29 to 2.25), lisinopril (HR, 1.28; 95% CI, 0.98 to 1.67), and quinapril (HR, 1.58; 95% CI, 1.10 to 2.82) were associated with higher mortality than was ramipril. No statistically significant difference was reported between perindopril and ramipril (HR, 0.98; 95% CI, 0.60 to 1.60). Secondary: Enalapril (HR, 1.44; 95% CI, 13 to 2.01) and fosinopril (HR, 1.83; 95% CI, 1.27 to 2.62) were associated with higher readmission rates for CHF than ramipril. Readmissions for unstable angina and recurrent MI were similar across all prescription groups.
Dalhof et al.[60] (2005) ASCOT-BPLA Amlodipine 5 to	MC, OL, RCT Patients 40 to 79 years of age with HTN and ≥3 other	N=19,257 5.5 years	Primary: Nonfatal MI (including silent MI) and fatal CHD	Primary: No statistically significant difference in nonfatal MI and fatal CHD was reported between the amlodipine plus perindopril group compared to the atenolol plus bendroflumethiazide groups (HR, 0.90; 95% CI, 0.79 to 12; P=0.1052).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
10 mg/day adding perindopril 4 to 8 mg/day as needed vs atenolol 50 to 100 mg/day adding bendro-flumethiazide* 1.25 to 2.5 mg/day and potassium as needed If blood pressure was still not achieved, doxazosin 4 to 8 mg/day was added to the regimen.	cardiovascular risk factors (left ventricular hypertrophy, other specified abnormalities on ECG, type 2 diabetes, PAD, history of stroke or TIA, male, age ≥55 years, microalbuminuria or proteinuria, smoking, TC:HDL-C ratio ≥6, or family history of CHD)		Secondary: All-cause mortality, total stroke, primary end points minus silent MI, all coronary events, total cardiovascular events and procedures, cardiovascular mortality, nonfatal and fatal heart failure, effects on primary end point and on total cardiovascular events and procedures among prespecified subgroups Tertiary: Silent MI, unstable angina, chronic stable angina, PAD, life-threatening arrhythmias, development of diabetes, development of renal impairment	Secondary: Significantly greater reductions in the following secondary end points were observed with amlodipine plus perindopril compared to atenolol plus bendroflumethiazide: all- cause mortality (P=0.0247), total stroke (P=0.0003), primary end points minus silent MI (P=0.0458), all coronary events (P=0.0070), total cardiovascular events and procedures (P<0.0001), and cardiovascular mortality (P=0.0010). There were no significant differences in nonfatal and fatal heart failure between the two treatment groups (P=0.1257). The study was terminated early due to higher mortality and worse outcomes on several secondary end points observed in the atenolol study group. Tertiary: Significantly greater reductions in the following end points were observed with amlodipine plus perindopril compared to atenolol plus bendroflumethiazide: unstable angina (P=0.0115), PAD (P=0.0001), development of diabetes (P<0.0001), and development of renal impairment (P=0.0187). There were no significant differences in the incidence of silent MI (P=0.3089), chronic stable angina (P=0.8323) or life-threatening arrhythmias (P=0.8009) between the two treatment groups. There was no significant difference in the percent of patients who stopped therapy because of an adverse event between the two treatment groups (overall 25%). There was, however, a significant difference in favor of amlodipine plus perindopril in the proportion of patients who stopped trial therapy because of a serious adverse events (2 vs 3%; P<0.0001).
Chapman et al.[61] (2007) ASCOT-BPLA	Subanalysis of ASCOT-BPLA evaluating effects of spironolactone on	N=1,411 1.3 years	Primary: Change in DBP and SBP, adverse effects	Primary: Spironolactone-treated patients lead to a significant 21.9 mm Hg reduction in SBP among patients whose blood pressure was previously uncontrolled on at least three other antihypertensive drugs (95% CI, 20.8 to 23.0 mm

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Atenolol 50 to 100 mg titrated to target blood pressure <140/90 mm Hg (or <130/90 mm Hg in diabetic patients); bendro-flumethiazide* plus potassium 1.25 to 2.5 mg plus doxazosin were added for additional blood pressure control; if blood pressure remained elevated on the 3 above drugs, spironolactone 25 mg was added to the regimen vs amlodipine 5 to 10 mg titrated to target blood pressure <140/90 mm Hg (or <130/90 mm Hg in diabetic patients); perindopril 4 to 8 mg and doxazosin were added for additional control;	treatment-resistant HTN Patients 40 to 79 years of age with HTN and ≥3 cardiovascular risk factors, with SBP ≥160 mm Hg and/or DBP ≥100 mm Hg (not on antihypertensive therapy) or SBP ≥140 mm Hg and/or DBP ≥90 mm Hg (on antihypertensive therapy)		Secondary: Not reported	Hg; P<0.001). Spironolactone-treated patients lead to a significant 9.5 mm Hg reduction in DBP among patients whose blood pressure was previously uncontrolled on at least three other antihypertensive drugs (95% CI, 9.0 to 10.1; P<0.001). Spironolactone-treated patients exhibited small but significant decreases in sodium, LDL-C and TC as well as increases in potassium, glucose, creatinine and HDL-C (P<0.05). The most common adverse effect reported in the trial was gynecomastia in men (P value not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
if blood pressure remained elevated on the 3 above drugs, spironolactone 25 mg was added to the regimen				
Pepine et al.[62] (2003) INVEST Verapamil SR 240 mg/day (step 1), then add trandolapril if needed (step 2), then increase doses of both (step 3), then add HCTZ (step 4) (calcium antagonist strategy) vs atenolol 50 mg/day (step 1), then add HCTZ if needed (step 2), then increase doses of both (step 3), then add trandolapril (step 4) (non-calcium antagonist strategy)	MC, OL, RCT Patients with essential HTN	N=22,576 24 months	Primary: First occurrence of death (all cause), nonfatal MI or stroke Secondary: Cardiovascular death, angina, cardiovascular hospitalization, angina, blood pressure control (SBP/DBP <140/90 mm Hg or <130/85 mm Hg if diabetic or renal impairment), safety	Primary: At 24 months, in the calcium antagonist strategy subgroup, 81.5% of patients were taking verapamil SR, 62.9% trandolapril, and 43.7% HCTZ. In the non-calcium antagonist strategy, 77.5% of patients were taking atenolol, 60.3% HCTZ, and 52.4% trandolapril. After a follow-up of 61,835 patient-years (mean, 2.7 years per patient), 2,269 patients had a primary outcome event with no statistically significant difference between treatment strategies (9.93% in calcium antagonist strategy vs 10.17% in non-calcium antagonist strategy; RR, 0.98; 95% CI, 0.90 to 16; P=0.57). Secondary: There was no significant difference in the rate of cardiovascular death (P=0.94) or cardiovascular hospitalization (P=0.59) between the two treatment groups. At 24 months, angina episodes decreased in both groups, but the mean frequency was lower in the calcium antagonist strategy group (0.77 episodes/week) compared to the non-calcium antagonist strategy group (0.88 episodes/week; P=0.02). Two-year blood pressure control was similar between groups. The blood pressure goals were achieved by 65.0% (systolic) and 88.5% (diastolic) of calcium antagonist strategy patients and 64.0% (systolic) and 88.1% (diastolic) of non-calcium antagonist strategy patients. A total of 71.7% of calcium antagonist strategy patients and 70.7% of non-calcium antagonist strategy patients achieved an SBP <140 mm Hg and DBP <90 mm Hg. Both regimens were generally well tolerated. Patients in the calcium

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Trandolapril was recommended for all patients with heart failure, diabetes, or renal insufficiency.				antagonist strategy group reported constipation and cough more frequently than patients in the non-calcium antagonist strategy group, while non-calcium antagonist strategy patients experienced more dyspnea, lightheadedness, symptomatic bradycardia and wheezing (all were statistically significant with P≤0.05).
Lindholm et al.[63] (2005) Other antihypertensive therapies (amiloride, amlodipine, bendro-flumethiazide*, captopril, diltiazem, enalapril, felodipine, HCTZ, isradipine, lacidipine, lisinopril, losartan, or verapamil) or placebo vs β-blocker therapy (atenolol, metoprolol, oxprenolol*, pindolol, or	MA 13 RCTs evaluating the treatment of primary HTN with a β-blocker as first-line treatment (in ≥50% of all patients in one treatment group) and outcome data for all-cause mortality, cardiovascular morbidity or both	N=105,951 2.1 to 10.0 years	Primary: Stroke, MI, all-cause mortality Secondary: Not reported	Primary: The RR of stroke was 16% higher with β-blocker therapy than for the comparator therapies (RR, 1.16; 95% CI, 1.04 to 1.30; P=0.009). The RR of stroke was the highest with atenolol (26% higher) compared to other non β-blockers (RR, 1.26%; 95% CI, 15 to 38; P<0.0001). The relative risk of MI was 2% higher for β- blocker therapy than for the comparator therapies (RR, 1.02; 95% CI, 0.93 to 1.12), which was not significant (P value not reported). The RR of all-cause mortality was 3% higher for β-blocker therapy than for the comparator therapies (RR, 1.16; 95% CI, 0.99 to 1.08; P=0.14). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
propranolol)				
Wiysonge et al.[64] (2007) Other antihypertensive therapies (i.e., placebo, diuretics, calcium channel blockers, or renin-angiotensin system inhibitors) vs β-blockers (atenolol, metoprolol, oxprenolol*, or propranolol)	MA 13 RCTs evaluating patients ≥18 years of age with HTN	N=91,561 Duration varied	Primary: All-cause mortality Secondary: Stroke, CHD, cardiovascular death, total cardiovascular disease, adverse reactions	Primary: There was not a significant difference observed in all-cause mortality between β-blocker therapy and placebo (RR, 0.99; 95% CI, 0.88 to 1.11; P value not reported), diuretics (RR, 1.04; 95% CI, 0.91 to 1.19; P value not reported) or renin-angiotensin system inhibitors (RR, 1.10; 95% CI, 0.98 to 1.24; P value not reported). There was a significantly higher rate in all-cause mortality with β-blocker therapy compared to calcium channel blockers (RR, 1.07; 95% CI, 1.00 to 1.14; P=0.04). Secondary: There was a significant decrease in stroke observed with β-blocker therapy compared to placebo (RR, 0.80; 95% CI, 0.66 to 0.96). Also there was a significant increase in stroke with β-blocker therapy compared to calcium channel blockers (RR, 1.24; 95% CI, 1.11 to 1.40) and renin-angiotensin system inhibitors (RR, 1.30; 95% CI, 1.11 to 1.53), but there was no difference observed compared to diuretics (RR, 1.17; 95% CI, 0.65 to 2.09). CHD risk was not significantly different between β-blocker therapy and placebo (RR, 0.93; 95% CI, 0.81 to 1.07]), diuretics (RR, 1.12; 95% CI, 0.82 to 1.54), calcium channel blockers (RR, 1.05; 95% CI, 0.96 to 1.15) or renin-angiotensin system inhibitors (RR, 0.90; 95% CI, 0.76 to 1.06). The risk of total cardiovascular disease was lower with β-blocker therapy compared to placebo (RR, 0.88; 95% CI, 0.79 to 0.97). The effect of β-blocker therapy on cardiovascular disease was significantly worse than that of calcium channel blockers (RR, 1.18; 95% CI, 1.08 to 1.29), but was not significantly different from that of diuretics (RR, 1.13; 95% CI, 0.99 to 1.28) or renin-angiotensin system inhibitors (RR, 1.00; 95% CI, 0.72 to 1.3). There was a significantly higher rate of discontinuation due to side effects with β-blocker therapy compared to diuretics (RR, 1.86; 95% CI, 1.39 to 2.50) and renin-angiotensin system inhibitors (RR, 1.41; 95% CI, 1.29 to 1.54), but there was no significant difference compared to calcium channel blockers (RR, 1.20; 95% CI, 0.71 to 2.04). Actual side effects were not

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				reported.
Blood Pressure Lowering Treatment Trialists' Collaboration[65] (2007) ACE inhibitors (17 trials) vs ARBs (9 trials)	MA Patients with high blood pressure, diabetes, history or CHD or cerebrovascular disease	N=146,838 (26 trials) Variable duration	Primary: Nonfatal myocardial infarction or death from CHD, including sudden death; heart failure causing death or requiring hospitalization; nonfatal stroke or death from cerebrovascular disease Secondary: Not reported	Primary: From a total of 146,838 individuals with high blood pressure or an elevated risk of cardiovascular disease, major cardiovascular events were documented in 22,666 patients during follow-up. The analyses showed comparable blood pressure-dependent reductions in risk with ACE inhibitors and ARBs (P≥0.3 for all three outcomes). ACE inhibitors produced a blood pressure-independent reduction in the relative risk of CHD of approximately 9% (95% CI, 3 to 14%). No similar effect was detected for ARBs, and there was some evidence of a difference between ACE inhibitors and ARBs in this regard (P=0.002). For both stroke and heart failure, there was no evidence of any blood pressure-independent effects of either ACE inhibitors or ARBs. Secondary: Not reported
Cerebrovascular Disease				
PROGRESS[66] (2001) Perindopril 4 mg/day vs perindopril 4 mg/day and indapamide 2 to 2.5 mg/day vs placebo	DB, MC, PC, RCT Patients with a history of prior stroke or TIA within the previous 5 years	N=6,105 4 years	Primary: Fatal or nonfatal stroke Secondary: Fatal or disabling stroke, total major vascular events comprising the composite of nonfatal stroke, nonfatal MI, or death due to any vascular cause (including unexplained sudden death); total and cause	Primary: Patients receiving active treatment experienced a 28% reduction in nonfatal or fatal stroke (95% CI, 17 to 38; P<0.0001). There were similar reductions in the risk of stroke in hypertensive and non-hypertensive subgroups (32 vs 27%; P<0.01) A trend towards a greater effect of active treatment among patients treated with combination therapy (43% risk reduction) than in those treated with single drug therapy (5% risk reduction) was reported. Secondary: There was a 33% reduction in fatal or disabling strokes in the active treatment group. Active treatment reduced the risk of total major vascular events by 26% (P=0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			specific deaths; hospital admissions	There were no significant differences between active treatment and placebo in total deaths from vascular or nonvascular causes. Among those assigned active treatment, there was a 9% RR reduction in hospitalization, with a median reduction of 2.5 days in the time spent in the hospital during follow-up. Combination therapy with perindopril plus indapamide reduced blood pressure by 12/5 mm Hg and stroke risk by 43%. Single drug therapy reduced blood pressure by 5/3 mm Hg and produced no discernible reduction in the risk of stroke.
Arima et al.[67] (2011) PROGRESS Perindopril 4 mg/day vs perindopril 4 mg/day and indapamide 2 to 2.5 mg/day vs placebo	Post-hoc analysis Patients with a history of prior stroke or TIA within the previous 5 years	N=4,283 4 years	Primary: Total major vascular events (nonfatal stroke, nonfatal MI, or vascular death) Secondary: Not reported	Primary: Among all patients, active treatment reduced the RR of major vascular events by 27% (95% CI, 10 to 41) in patients with isolated systolic HTN, by 28% (95% CI, -29 to 60) in patients with isolated diastolic HTN, and by 32% (95% CI, 17 to 45%) in patients with systolic-diastolic HTN. There was no evidence of differences in the magnitude of the effects of treatment among different types of HTN. Blood pressure reductions and RRs were consistently greater with combination therapy compared to single drug therapy (mean SBP difference, 12.3 vs 3.9 mm Hg, 7.7 vs 4.3 mm Hg, and 13.5 vs 5.2 mm Hg; RR reduction of major vascular events 34 vs 16%, 63 vs -78%, and 45 vs 10% for isolated systolic HTN, isolated diastolic HTN, and systolic-diastolic HTN). Secondary: Not reported
Heart Failure				
Pfeffer et al.[68] (1992) SAVE Captopril up to 50 mg TID vs	DB, MC, PC, RCT Patients 21 to 80 years of age who had an acute MI within 3 to 16 days and left ventricular dysfunction with a	N=2,231 42 months (average)	Primary: Mortality from all causes, mortality from cardiovascular causes, mortality combined with a decrease in	Primary: Mortality from all causes was significantly reduced in the captopril group (20%) vs placebo group (25%) for a 19% reduction in the risk of mortality from all causes (95% CI, 3 to 25; P=0.019). The incidence of fatal cardiovascular events was consistently reduced in the captopril group with a 21% reduced risk of mortality from cardiovascular causes (P=0.014).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	LVEF ≤40%, but without overt heart failure or symptoms of myocardial ischemia		ejection fraction ≥9 units, cardiovascular morbidity, combination of cardiovascular mortality and morbidity Secondary: Not reported	The incidence of nonfatal major cardiovascular events was consistently reduced in the captopril group with a 25% reduced risk of recurrent MI (P=0.015), 37% reduced risk for the development of severe heart failure (P<0.001), and 22% reduced risk of CHF requiring hospitalization (P=0.019). Long-term captopril administration was associated with an improvement in survival and reduced morbidity and mortality due to major cardiovascular events. Secondary: Not reported
Pitt et al.[69] (1997) ELITE Captopril 50 mg TID vs losartan 50 mg QD	DB, MC, PG, RCT Patients ≥65 years with symptomatic heart failure (NYHA class II to IV and LVEF ≤40%), and no history of prior ACE inhibitor therapy	N=722 1 year	Primary: Change in renal function Secondary: Composite of death and/or hospital admission for heart failure, all-cause mortality, admission for heart failure, NYHA class, admission for MI or unstable angina	Primary: No difference between losartan and captopril was reported in the rate of persistent rise in serum creatinine concentrations (10.5% for both groups). Secondary: Death and/or hospital admission for heart failure was recorded in 9.4% of patients receiving losartan and 13.2% for patients receiving captopril (risk reduction, 32%; 95% CI, -4 to 55; P=0.075). This risk reduction was primarily due to a decrease in all-cause mortality (4.8 vs 8.7%; risk reduction, 46%; 95% CI, 5 to 69; P=0.035). Admissions with heart failure were the same in both groups (5.7%), as was improvement in NYHA functional class from baseline. Admission to hospital for any reason was less frequent with losartan than with captopril treatment (22.2 vs 29.7%; P=0.014). More patients discontinued therapy due to adverse events with captopril (20.8%) than losartan (12.2%; P=0.002).
Pitt et al.[70] (2000) ELITE II Captopril 50 mg TID	DB, MC, PG, RCT Patients ≥60 years old with symptomatic heart failure (NYHA II to	N=3,152 555 days (mean follow-up)	Primary: All-cause mortality Secondary: Composite of sudden cardiac	Primary: No significant difference in all-cause mortality was reported between losartan (17.7%) and captopril (15.9%; HR, 1.13; 95% CI, 0.95 to 1.35; P=0.16). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs losartan 50 mg QD	IV and LVEF ≤40%), and no history of prior ACE inhibitor therapy		death or resuscitated cardiac arrest	Sudden death or resuscitated cardiac arrest was observed in 9.0% of patients receiving losartan and 7.3% of patients receiving captopril (HR, 1.25; 95% CI; 0.98 to 1.60; P=0.08). Significantly fewer patients in the losartan group (excluding those who died) discontinued study treatment because of adverse events (9.7 vs 14.7%; P<0.001), including cough (0.3 vs 2.7%). Note: ELITE II trial was a larger follow-up trial to the ELITE I trial to confirm the secondary end point from the ELITE I trial, which reported a greater reduction in all-cause mortality with losartan compared to captopril.
Dickstein et al.[71] (2002) OPTIMAAL Captopril 50 mg TID vs losartan 50 mg QD	DB, MC, PG, RCT Patients ≥50 years with an acute MI and signs or symptoms of heart failure during the acute phase or a new Q-wave anterior infarction or reinfarction	N=5,477 2.7 years (mean)	Primary: All-cause mortality Secondary: Composite of sudden cardiac death or resuscitated cardiac arrest	Primary: No significant difference in all-cause mortality was reported between patients receiving losartan and captopril (18 vs 16%, respectively; RR, 1.13; 95% CI, 0.99 to 1.28; P=0.07). Secondary: No significant difference in sudden cardiac death or resuscitated cardiac arrest was reported between patients receiving losartan and captopril (9% vs 7; RR, 1.19; 95% CI, 0.98 to 1.43; P=0.07). Losartan was significantly better tolerated than captopril, with fewer patients discontinuing study medication (17 vs 23%; P<0.0001).
Pfeffer et al.[72] (2003) VALIANT Captopril 50 mg TID vs valsartan 160 mg BID vs	DB, MC, RCT Patients ≥18 years of age with an acute MI that was complicated by clinical or radiologic signs of heart failure and/or evidence of left ventricular systolic dysfunction	N=14,703 24.7 months	Primary: All-cause mortality Secondary: Death from cardiovascular causes, recurrent MI, hospitalization for heart failure	Primary: No significant difference in all-cause mortality was reported between valsartan monotherapy and captopril monotherapy (P=0.98). No significant difference in all-cause mortality was observed between valsartan plus captopril combination therapy and captopril monotherapy (P=0.73). Secondary: The rate of death from cardiovascular causes, reinfarction, or hospitalization for heart failure was not significantly different between valsartan and captopril monotherapy (P=0.20).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
valsartan 80 mg BID and captopril 50 mg TID				The rate of death from cardiovascular causes, reinfarction, or hospitalization for heart failure was not significantly different between valsartan and captopril combination therapy and captopril monotherapy (P=0.37). Combination therapy had the most drug-related adverse events. With monotherapy, hypotension and renal dysfunction were more common in the valsartan group and cough, rash, and taste disturbance were more common in the captopril group.
CONSENSUS Trial Study Group[73] (1987) CONSENSUS Enalapril 2.5 to 40 mg/day vs placebo	DB, MC, PC, PG, RCT Patients with severe CHF (NYHA class IV symptoms), patients with recent MI and unstable angina were excluded	N=253 188 days (average)	Primary: 6-month mortality and the cause of death Secondary: 12-month mortality and overall mortality	Primary: Mortality at six months was 26 and 44% for patients in the enalapril and placebo groups, respectively, for an overall reduction of 40% for enalapril (P=0.002). Secondary: At 12 months, enalapril reduced mortality by 31% compared to placebo (P=0.001). By the end of the study, there had been 50 deaths in the enalapril group and 68 deaths in the placebo group for a reduction of 27% (P=0.003). The entire reduction in total mortality was found to be among patients with progressive heart failure (a reduction of 50%), whereas no difference was seen in the incidence of sudden cardiac death. Note: The study was stopped early due to clear benefit with enalapril.
SOLVD Investigators[74] (1991) SOLVD Enalapril 2.5 to 20 mg/day vs placebo	DB, MC, PC, RCT Patients with CHF and LVEF ≤35% receiving conventional therapy	N=2,569 41.4 months (average)	Primary: Mortality, rate of hospitalization for heart failure Secondary: Not reported	Primary: Death was reported in 35.2 and 39.7% of patients receiving enalapril and placebo, respectively (risk reduction, 16%; 95% CI, 5 to 26; P=0.0036). Although reductions in mortality were observed in several categories of cardiac deaths, the largest reduction occurred among the deaths attributed to progressive heart failure (risk reduction, 22%; 95% CI, 6 to 35). There was little apparent effect of treatment on deaths classified as due to arrhythmia without pump failure. Fewer patients died or were hospitalized for worsening heart failure (risk reduction, 26%; 95% CI, 18 to 34; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
SOLVD Investigators[75] (1992) SOLVD Enalapril 2.5 mg to 20 mg/day vs placebo	DB, MC, PC, RCT Patients 21 to 80 years of age with heart disease and an ejection fraction of ≤35% who were not receiving diuretics, digoxin or vasodilators for the treatment of heart failure	N=4,228 37.4 months (average)	Primary: All-cause mortality, incidence of heart failure, rate of hospitalization for heart failure Secondary: Not reported	Primary: Enalapril resulted in an 8% reduction in risk for all-cause mortality (P=0.30). The difference was entirely due to a reduction in deaths due to cardiovascular causes, primarily progressive heart failure (risk reduction, 12%; P=0.12). In the placebo group, 30.2% of patients developed heart failure compared to 20.7% for enalapril (risk reduction, 37%; P<0.001). Rates of first hospitalization and multiple hospitalizations for CHF were higher with placebo (12.9 and 4.8%) than enalapril (8.7 and 2.7%; both P<0.001). The total number of deaths and cases of heart failure were lower in the enalapril group than in the placebo group (risk reduction, 29%; P<0.001). In addition, fewer patients given enalapril died or were hospitalized for heart failure (risk reduction, 20%; P<0.001). Secondary: Not reported
McMurray et al.[76] (2016) ATMOSPHERE Enalapril 5 or 10 mg BID vs aliskiren 150 mg QD vs	DB, DD, RCT Patients with CHF (NYHA class II to IV) and EF ≤35% receiving stable doses of an ACE inhibitor (equivalent to at least 10 mg of enalapril daily) and of a β-blocker at the time of enrollment	N=7,016 Median of 36.6 months	Primary: Composite of death from cardiovascular causes or hospitalization for heart failure Secondary: Change from baseline to 12 months in the Kansas City Cardiomyopathy	Primary: Overall, the primary outcome occurred in 770 patients (32.9%) in the combination-therapy group (11.7 events per 100 person-years), in 791 patients (33.8%) in the aliskiren group (12.1 events per 100 person-years), and in 808 patients (34.6%) in the enalapril group (12.4 events per 100 person-years). The HR in the combination-therapy group, as compared with the enalapril group, was 0.93 (95% CI, 0.85 to 1.03; P=0.17); the HR in the aliskiren group, as compared with the enalapril group, was 0.99 (95% CI, 0.90 to 1.10; P=0.91 for superiority). Although the noninferiority margin of 1.104 was met with the use of the 95% confidence interval, the one-sided P value of 0.0184 did not fulfill the prespecified requirement of a P value of 0.0123 or less. A sensitivity analysis that included only patients who received the assigned trial regimen gave consistent results, as did an analysis in which data that were collected after regulatory censoring

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
combination of aliskiren 150 mg QD and enalapril 5 or 10 mg BID			Questionnaire (KCCQ) clinical summary score	were included. Secondary: There were no significant between-group differences in the secondary outcome. The exploratory composite renal outcome (the composite of death from renal causes, end-stage renal disease, or doubling of the serum creatinine level) occurred significantly more frequently in the combination-therapy group than in the enalapril group.
McKelvie et al.[77] (1999) RESOLVD Enalapril 10 mg BID vs candesartan 4 to 16 mg QD vs candesartan 4 to 8 mg QD and enalapril 10 mg BID	DB, PG, MC, RCT Patients with CHF (NYHA classes II to IV), a 6 minute walk distance of 500 meters or less, and an ejection fraction <40%	N=768 43 weeks	Primary: Change in 6-minute walk distance Secondary: Change in NYHA functional class, QOL, ejection fraction, ventricular volumes, neurohormone levels, safety	Primary: There were no significant differences among the groups with regards to the 6-minute walk distance over the 43 week study period. Secondary: There were no significant differences among the groups with regards to the NYHA functional class or QOL at 18 or 43 weeks. Ejection fraction increased more with candesartan plus enalapril than monotherapy with either agent; however, the difference was not statistically significant (P value not significant). End-diastolic volumes (P<0.01) and end-systolic volumes (P<0.05) increased less with combination therapy than with monotherapy with either agent. Aldosterone decreased with combination therapy at 17 but not 43 weeks compared to candesartan or enalapril (P<0.05). Brain natriuretic peptide decreased with combination therapy compared to candesartan and enalapril alone (P<0.01). Blood pressure decreased with combination therapy compared to candesartan or enalapril alone (P<0.05). Compared to enalapril, potassium decreased with candesartan use (P<0.05) and increased with candesartan plus enalapril (P<0.05). The proportion of patients with potassium levels ≥5.5 mmol/L was not significantly different among the treatment groups. There were no significant differences in creatinine, mortality, or hospitalizations for CHF or any cause among the three groups.
Willenheimer et	BE, MC, OL, PG,	N=1,010	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
al.[78] (2005) CIBIS-III Enalapril 2.5 to 10 mg BID vs bisoprolol 1.25 to 10 mg QD	RCT Patients ≥65 years with stable mild to moderate CHF (NYHA class II to III), LVEF of ≤35% ≥3 months prior to randomization, not on an ACE inhibitor, β-blocker or ARB therapy and no clinically relevant fluid retention of diuretic adjustment within the 7 days prior to randomization	1.22±0.42 years	Combined all-cause mortality or hospitalization Secondary: Combined end point at the end of the monotherapy phase and the individual components of the primary end point, cardiovascular death and cardiovascular hospitalization, permanent treatment cessation and the need for early introduction of the second drug as indicators of drug tolerability	There were 178 patients (35.2%) with a primary end point of combined all-cause mortality or all-cause hospitalization in the bisoprolol-first group, compared to 186 (36.8%) patients in the enalapril-first group (absolute difference, -1.6%; 95% CI, -7.6 to 4.4; HR, 0.94; 95% CI, 0.77 to 1.16; non-inferiority for bisoprolol-first vs enalapril-first treatment; P=0.019). Secondary: The combined endpoint at the end of the monotherapy phase occurred in 109 patients in the bisoprolol-first group compared to 108 patients in the enalapril-first group (HR, 1.02; 95% CI, 0.78 to 1.33; between-group difference P=0.90); 23 vs 32 patients died, respectively (HR, 0.72; 95% CI, 0.42 to 1.24; between-group difference P=0.24); and 99 vs 92 patients had been a hospitalization, respectively (HR, 1.08; 95% CI, 0.81 to 1.43; between-group difference P=0.59). There were 65 deaths in the bisoprolol-first group, as compared to 73 in the enalapril-first group (HR, 0.88; 95% CI, 0.63 to 1.22; between-group difference P=0.44). In the bisoprolol-first group, 151 patients were hospitalized, compared to 157 patients in the enalapril-first group (HR, 0.95; 95% CI, 0.76 to 1.19; between-group difference P=0.66). There was not a significant difference in cardiovascular death rate observed between the bisoprolol-first (55) and enalapril-first (56) treatment groups (HR, 0.97; 95% CI, 0.67 to 1.40; between-group difference P=0.86). During the monotherapy phase, 35 (6.9%) patients in the bisoprolol-first group permanently discontinued therapy, compared to 49 (9.7%) patients in the enalapril-first group. During the combined-therapy phase, 19 patients (4.2%) in the bisoprolol-first group permanently discontinued bisoprolol therapy and 47 (10.4%) discontinued enalapril therapy. In the enalapril-first group, 24 patients (5.5%) permanently discontinued bisoprolol and 16 (3.7%) discontinued enalapril.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was not a statistical significant difference observed in the early introduction of the second drug between the bisoprolol-first group (39 [7.7%] patients) compared to the enalapril-first group (37 [7.3%] patients; P=0.81).
Cohn et al.[79] (1991) V-HEFT II Enalapril 20 mg/day vs hydralazine 300 mg plus isosorbide dinitrate 160 mg/day	AC, DB, MC, RCT Men between the ages of 18 and 75 years with chronic heart failure receiving digoxin and diuretic therapy	N=804 2 years	Primary: Mortality Secondary: Peak oxygen consumption during exercise, LVEF	Primary: Mortality after two years was significantly lower in the group treated with enalapril (18%) than hydralazine plus isosorbide dinitrate (25%; P=0.016), and overall mortality tended to be lower (P=0.08). The lower mortality in the enalapril arm was attributable to a reduction in the incidence of sudden death, and this beneficial effect was more prominent in patients with less severe symptoms (NYHA class I or II). Secondary: Peak oxygen consumption during exercise was increased only by hydralazine plus isosorbide dinitrate (P<0.05). While LVEF increased with both regimens during the two years after randomization, LVEF increased more (P<0.05) during the first 13 weeks in the hydralazine plus isosorbide dinitrate group.
Tu et al.[80] (2005) Enalapril vs lisinopril, ramipril, and other ACE inhibitors (benazepril, captopril, cilazapril*, fosinopril, perindopril, quinapril, and trandolapril)	RETRO Patients >65 years with newly diagnosed CHF initiated on ACE inhibitors who survived ≥30 days after hospital discharge	N=6,753 ≤2 years	Primary: Combined end point of readmission for CHF as a primary diagnosis or mortality Secondary: CHF readmission alone and mortality alone	Primary: Relative to enalapril users, there were no significant differences in combined end point of readmission for CHF or mortality with lisinopril (adjusted HR, 18; 95% CI, 0.94 to 1.23), ramipril (adjusted HR, 16; 95% CI, 0.92 to 1.24) or other ACE inhibitors (adjusted HR, 12; 95% CI, 0.90 to 1.17). Secondary: There were no significant differences among groups in readmission for CHF: enalapril 13% (adjusted HR, 1), lisinopril 15% (adjusted HR, 1.11; 95% CI, 0.92 to 1.32), ramipril 15% (adjusted HR, 1.19; 95% CI, 0.99 to 1.45), and other ACE inhibitors 15% (adjusted HR, 1.13; 95% CI, 0.96 to 1.34). There were no significant differences among groups in mortality: enalapril 12% (adjusted HR, 1), lisinopril 13% (adjusted HR, 19; 95% CI, 0.90 to 1.31), ramipril 12% (adjusted HR, 0.97; 95% CI, 0.78 to 1.20), and other

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				ACE inhibitors 11% (adjusted HR, 0.94; 95% CI, 0.78 to 1.13).
Packer et al.[81] (1999) ATLAS Lisinopril 2.5 to 5 mg/day (low dose) vs lisinopril 32.5 to 35 mg/day (high dose)	DB, RCT Patients with NYHA class II, III, or IV symptoms of heart failure associated with a LVEF ≤30% despite treatment with diuretics for ≥2 months	N=3,164 39 to 58 months	Primary: All-cause mortality Secondary: cardiovascular mortality, hospitalizations (for any reason and for cardiovascular reasons), combinations of the primary and secondary end points	Primary: High-dose lisinopril was associated with a nonsignificant 8% lower risk of all-cause mortality compared to low-dose lisinopril (P=0.128). Secondary: Cardiovascular mortality was reported in 40.2 and 37.2% of patients receiving low-dose and high-dose lisinopril, respectively (P=0.073). High-dose lisinopril resulted in a 12% lower risk of death or hospitalizations for any reason (P=0.002), a 9% lower risk of cardiovascular mortality and hospitalization for cardiovascular reason (P=0.027) and 24% fewer hospitalizations for heart failure (P=0.002). Dizziness and renal insufficiency were observed more frequently in the high-dose group, but the two groups were similar in the number of patients requiring discontinuation of the study medication.
AIRE Study Investigators[82] (1993) AIRE Ramipril 2.5 to 5 mg BID vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with acute MI and clinical evidence of heart failure	N=2,006 15 months	Primary: All-cause mortality Secondary: First event in an individual patient (death, progression to severe or resistant heart failure, reinfarction, or stroke)	Primary: On the intention-to-treat analysis, all-cause mortality was significantly lower for patients randomized to receive ramipril (17%) than placebo (23%). The observed risk reduction was 27% (95% CI, 11 to 40; P=0.002). Secondary: Analysis of prespecified secondary outcomes revealed a 19% risk reduction in the ramipril group compared to placebo (95% CI, 5 to 31; P=0.008).
Wu et al.[83] (2021) AIRE-S (AIRE survival) Ramipril target dose 10 mg/day	DB, MC, PC, PG, RCT Patients ≥18 years of age with acute MI and clinical evidence of heart failure	N=603 29.6 years	Primary: All-cause mortality for UK participants Secondary: Life expectancy and extensions of life (difference	Primary: By April 9, 2019, death from all causes occurred in 266 (88.4%) patients in placebo arm and 275 (91.1%) patients in ramipril arm. Survival at the end of study follow-up was not different between the ramipril and placebo groups (HR, 0.96; 95% CI, 0.81 to 1.15) because more-or-less all patients had died at the end of follow-up. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo			in median survival times)	Ramipril treatment improved life expectancy across all of the comorbidity groups studied, including diabetes (LED, 32.1 vs 5.0 months), previous MI (20.1 vs 4.9 months), history of heart failure (19.5 vs 4.9 months), hypertension (16.6 vs 8.3 months), angina (16.2 vs 5.0 months) and was greater for patients aged ≥65 years than <65 years (11.3 vs 5.7 months). The median survival time was 8.3 years (95% CI, 6.2 to 10.2 years) for placebo group and 9.6 years (95% CI, 8.3 to 10.9 years) for ramipril group. The extension of life between ramipril and placebo groups, measured by the difference in median survival time, was 14.5 (95% CI, 13.2 to 15.8) months.
Kober et al.[84] (1995) TRACE Trandolapril 1 to 4 mg QD vs placebo Medication was started between day 3 and 7 after the myocardial infarction.	DB, MC, PC, RCT Men and women >18 years who were hospitalized with a recent MI and an LVEF ≤35%	N=1,749 24 to 50 months	Primary: Death from any cause Secondary: Death from a cardiovascular cause, sudden death, progression to severe heart failure (defined as the first of the following events: hospital admission for heart failure, death due to progressive heart failure, or heart failure necessitating the administration of open-label ACE inhibition), recurrent infarction, change in the wall-motion index	Primary: During the study, 34.7% of patients in the trandolapril group died compared to 42.3% in the placebo group (P=0.001). The relative risk of death in the trandolapril group was 0.78 compared to placebo (95% CI, 0.67 to 0.91). Secondary: Trandolapril reduced the risk of death from cardiovascular causes (RR, 0.75; 95% CI, 0.63 to 0.89; P=0.001) and sudden death (RR, 0.76; 95% CI, 0.59 to 0.98; P=0.03). Progression to severe heart failure was less frequent in the trandolapril group (RR, 0.71; 95% CI, 0.56 to 0.89; P=0.003). The risk of recurrent fatal or nonfatal MI was not significantly reduced (RR, 0.86; 95% CI, 0.66 to 1.13; P=0.29). After three months, the mean change from the base-line index was 0.09 in the trandolapril group and 0.06 in the placebo group (P=0.03) but this statistically significant difference was absent at six and 12 months.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Galløe et al.[85] (2006) Trandolapril 0.5 mg (0, 1, 2 or 4 tablets QD) plus bumetanide 0.5 mg (0, 1, 2 or 4 tablets BID) Treatment was combined to achieve 16 different dosage combinations.	DB, DD, RCT, multiple XO Patients with previous MI ≥3 years ago, had medical treatment for heart failure and ejection fraction between 0.36 and 0.54 estimated by echocardiography	N=16 14 days	Primary: Patient reported QOL Secondary: Effects on kidney function, left ventricular function and blood pressure	Primary: Bumetanide 0.5 mg-treated patients experienced a 12% increase in well-being, but higher doses of bumetanide decreased patient's well-being by 12% compared to placebo (P<0.002). Increasing doses of bumetanide tended to increase tiredness (P=0.072). There were no significant effects of bumetanide therapy on the patients' opinion of their health, degree of dyspnea, appetite or work capacity. Secondary: Bumetanide therapy increased 24 hour urine production in a straight dose-dependent manner (P<0.0001), while trandolapril therapy had no effect (P=0.53). Bumetanide and trandolapril therapy did not alter the 24 hour creatinine excretion and creatinine clearance (P=0.33, P=0.11 and P=0.53, P=0.97, respectively). Bumetanide therapy decreased left ventricular function and increased heart rate in a dose-dependent manner (P<0.001). Left ventricular function was also nonsignificantly decreased with trandolapril therapy (P>0.062). Trandolapril therapy significantly reduced SBP by maximally of 7.6 mm Hg (5.8%) with the lowest dose of 0.5 mg/day (P=0.007). Bumetanide therapy had no significant effect on DBP (P=0.23).
Galloe et al.[86] (2006) Trandolapril 0.5 mg (0, 1, 2, or 4 tablets QD) vs bumetanide 0.5 mg (0, 1, 2, or 4 tablets BID)	DB, PC, RCT, XO Men and women with previous MI ≥3 years ago, had medical treatment for heart failure and ejection fraction between 0.36 and 0.54 estimated by echo-cardiography (wall motion index)	N=16 14 days	Primary: Patient reported QOL Secondary: Effects on the involved organs: kidney function, left ventricular function, blood pressure	Primary: Patient's well-being increased 12% with 0.5 mg bumetanide BID but higher doses bumetanide decreased patient's well-being by 12% compared to placebo (P<0.002). Increasing doses of bumetanide tended to increase tiredness (P=0.072). There were no statistically significant effects of bumetanide on the patient's opinion of their health, degree of dyspnea, appetite or work capacity. Secondary: Bumetanide increased 24-hour urine production in a straight dose-dependent manner (P<0.0001) while trandolapril had no effect (P=0.53). Bumetanide and trandolapril did not alter the 24-hour creatinine excretion and creatinine clearance (P=0.33, P=0.11 and P=0.53, P=0.97, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Bumetanide decreased left ventricular function and increased heart rate in a dose dependent manner (P<0.001). Left ventricular function was also decreased with trandolapril but did not reach statistically significant. (P>0.062). Trandolapril significantly reduced SBP by maximally of 7.6 mm Hg (5.8%) with the lowest dose of 0.5 mg/day (P=0.007). Bumetanide had no significant effect on DBP (P=0.23).
Fröhlich et al.[87] (2018) Enalapril vs lisinopril vs ramipril Medication used was at the discretion of the referring physician.	Cohort Outpatients with stable HFrEF (EF <45%)	N=4,723 ≥6 months (Median follow-up of 50 months)	Primary: Mortality Secondary: Not reported	Baseline characteristics of HFrEF patients differed with respect to ACE inhibitor treatment for a number of variables. Overall, patients receiving ramipril were younger and more likely to have NYHA functional Class I or II symptoms than those on enalapril and lisinopril. NT-proBNP levels were lower in the ramipril group, whereas LVEF was similar in all three treatment groups. In patients using lisinopril, systolic BP was significantly higher when compared with patients on enalapril or ramipril. Primary: During a follow-up of 21,939 patient-years, 360 (49.5%), 337 (52.4%), and 1119 (33.4%) patients died among those prescribed enalapril, lisinopril, and ramipril, respectively. In univariable analysis of the general sample, enalapril and lisinopril were both associated with higher mortality when compared with ramipril treatment (HR, 1.46; 95% CI, 1.30 to 1.65; P<0.001; and HR, 1.38; 95% CI, 1.22 to 1.56; P<0.001, respectively). Patients prescribed enalapril or lisinopril had similar mortality (HR, 1.06; 95% CI, 0.92 to 1.24; P=0.41). However, there was no significant association between ACE inhibitor choice and all-cause mortality in any of the matched samples (HR, 1.07; 95% CI, 0.91 to 1.25; P=0.40; HR, 1.12; 95% CI, 0.96 to 1.32; P=0.16; and HR, 1.10; 95% CI, 0.93 to 1.31; P=0.25 for enalapril vs ramipril, lisinopril vs ramipril, and enalapril vs lisinopril, respectively). Results were confirmed in subgroup analyses with respect to age, sex, LVEF, New York Class Association functional class, cause of HFrEF, rhythm, and systolic BP. Secondary: Not reported
Lee et al.[88] (2004)	MA	N=38,080	Primary: All-cause mortality	Primary: ARBs were associated with reduced all-cause mortality (OR, 0.83) and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ARBs vs placebo (±ACE inhibitor) vs ACE inhibitor monotherapy	Patients with chronic heart failure and high-risk acute MI	Duration varied	and heart failure hospitalizations Secondary: Not reported	heart failure hospitalizations (OR, 0.64) vs placebo. There was no difference in all-cause mortality (OR, 1.06) and heart failure hospitalization (OR, 0.95) between ARBs and ACE inhibitors. When ARBs were combined with ACE inhibitors, all-cause mortality was not reduced (OR, 0.97) but heart failure hospitalizations were reduced (OR, 0.77) compared to treatment with ACE inhibitors alone. Two RCT comparing ARBs with ACE inhibitors in patients with high-risk acute MI did not reveal differences in all-cause mortality or heart failure hospitalization. Secondary: Not reported
Hypertension				
Kuschnir et al.[89] (1996) Benazepril 20 mg/day and amlodipine 5 mg/day vs amlodipine 5 mg/day vs benazepril 20 mg/day vs placebo	DB, MC, PC, PG, RCT Men and women 21 to 80 years of age with uncomplicated primary HTN	N=308 8 weeks	Primary: Reduction in mean sitting DBP, SBP and percentage of patients with DBP <90 mm Hg or a ≥10 mm Hg reduction Secondary: Not reported	Primary: All treatment groups significantly reduced mean sitting DBP compared to placebo (P<0.001). Combination therapy had significantly greater reductions in DBP -13.2 mm Hg; P<0.001) compared to amlodipine (-8.8 mm Hg) and benazepril (-6.7 mm Hg) monotherapy. Combination therapy had significantly greater reductions in SBP (-24.7 mm Hg; P<0.001) compared to amlodipine (-16.2 mm Hg) and benazepril (-12.4 mm Hg). Significantly more patients on combination therapy reached DBP <90 mm Hg or a ≥10 mm Hg reduction (87.0%; P≤0.005) compared to amlodipine (67.5%) and benazepril (53.3%) monotherapy. Adverse events considered to be drug related occurred in 15.6% of patients receiving combination therapy, 24.7% of patients receiving amlodipine monotherapy, 6.5% of patients on benazepril monotherapy and 11.7% of patients on placebo (P values not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Neutel et al.[90] (2005) SELECT Benazepril and amlodipine 20-5 mg/day (fixed dose combination product) vs amlodipine 5 mg/day vs benazepril 20 mg/day	DB, RCT Patients with stage 2 systolic HTN	N=443 8 weeks	Primary: Reduction in SBP, proportion of patients achieving blood pressure control Secondary: Not reported	Primary: Significantly greater SBP reductions were achieved with combination therapy compared to amlodipine or benazepril monotherapy (P<0.0001). Significantly more patients on combination therapy met blood pressure goals than on monotherapy (P<0.0001). No significant difference was noted in the incidence of adverse events. Adverse events were low in all three treatment arms, with less peripheral edema in the combination group than in the amlodipine-treated group. Secondary: Not reported
Chrysant[91] (2004) Amlodipine and benazepril 5-40 mg QD for 4 weeks, followed by 10-40 mg QD for 4 weeks (fixed-dose combination product) vs benazepril 40	DB, RCT Men and women (mean age 53 years) with mean sitting DBP ≥95 mm Hg not adequately controlled with benazepril 40 mg/day monotherapy	N=329 8 weeks	Primary: Reduction in mean sitting DBP and SBP, reduction in standing DBP and SBP, and change in heart rate, safety Secondary: Not reported	Primary: Combination therapy had significantly greater reductions in sitting SBP (-17 mm Hg; P<0.0001) compared monotherapy (-5 mm Hg). Combination therapy had significantly greater reductions in sitting DBP (-14 mm Hg; P<0.0001) compared to monotherapy (-7 mm Hg). Combination therapy had significantly greater reductions in standing SBP (-17 mm Hg; P<0.0001) compared to monotherapy (-6 mm Hg). Combination therapy had significantly greater reductions in standing DBP (-14 mm Hg; P<0.0001) compared to monotherapy (-7 mm Hg). No significant differences in heart rate were observed (P>0.05). No significant differences in adverse events were reported (P>0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day for 8 weeks				Secondary: Not reported
Fogari et al.[92] (1997) Benazepril 10 mg QD vs amlodipine and benazepril 2.5-10 to 5-10 mg QD (fixed-dose combination product)	DB, MC, PC, RCT Men and women 24 to 73 years of age (mean 55 years) with HTN inadequately controlled with ACE inhibitor monotherapy	N=448 8 weeks	Primary: Reduction in mean sitting DBP Secondary: Reduction in sitting SBP, standing DBP and SBP, and percentage of patients with DBP <90 mm Hg (deemed excellent response) or a ≥10 mm Hg reduction (deemed good response)	Primary: Significantly greater reductions in sitting DBP were observed with benazepril 10 mg and amlodipine 2.5 mg (-5.3 mm Hg, 97.5% CI, -8.3 to -2.4; P=0.0001) and benazepril 10 mg and amlodipine 5 mg (-4.5 mm Hg, 97.5% CI, -7.4 to -1.6; P=0.0006) compared to benazepril monotherapy. Secondary: Significantly greater reductions in sitting SBP were seen with benazepril 10 mg and amlodipine 2.5 mg (-7.9 mm Hg, 97.5% CI, -12.3 to -3.5; P=0.0001) and benazepril 10 mg and amlodipine 5 mg (-7.9 mm Hg, 97.5% CI, -12.2 to -3.6; P=0.0000) compared to benazepril monotherapy. Significantly greater reductions in standing DBP and SBP were also reported with the combination therapy compared to benazepril monotherapy (P≤0.001). Significantly more patients had excellent or good response with benazepril 10 mg and amlodipine 2.5 mg (69.2%; P=0.0004) and 10-5 mg (65.8%; P=0.02) compared to benazepril monotherapy (40.5%). Tolerability was good in the three treatment groups and no significant abnormal laboratory data was detected.
Chrysant et al.[93] (2012) Study 1: Benazepril 40 mg/day (Group 1) vs amlodipine and benazepril 5-40 mg/day, up	Post-hoc analysis of 2 trials Patients with HTN	N=1,013 14 weeks	Primary: Change in baseline mean sitting DBP and mean sitting SBP, rate of blood pressure control (<140/90 mm Hg), rate of blood pressure control (mean sitting DBP <90 mm Hg or ≥10 mm Hg decrease	Primary: Pooled results demonstrate that combination therapy resulted in significantly greater lowering of mean sitting DBP and mean seated SBP compared to benazepril or amlodipine (P<0.001). Amlodipine and benazepril 10-20 mg/day resulted in significantly greater blood pressure reductions in White patients (mean sitting DBP: 12.99 mm Hg; mean sitting SBP: 13.72 mm Hg) compared to Black patients (8.80 and 8.72 mm Hg) (P<0.004). Amlodipine and benazepril 10-40 mg/day resulted in similar reductions in blood pressure in both White and Black patients. The proportion of patients who achieved blood pressure control with amlodipine and benazepril 10-40 mg/day was similar between White and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
titrated to 10-40 mg/day after 4 weeks (fixed-dose combination product) (Group 2) Study 2: Amlodipine and benazepril 10-20 mg/day, uptitrated to 10-40 mg/day after 2 weeks (Group 3) vs amlodipine and benazepril 10-20 mg/day (fixed-dose combination product) (Group 4) vs amlodipine 10 mg/day (Group 5)			from baseline) Secondary: Safety	Black patients (60.7%), whereas with amlodipine and benazepril 10-20 mg/day the rate of control was higher with White patients (61.2 vs 39.4%; P<0.023). There was no difference in the proportion of patients who responded to treatment between Black and White patients with amlodipine and benazepril 10-40 mg/day (74.8 vs 77%; P<0.639). The proportion of patients who responded to amlodipine and benazepril 10-20 mg/day was significantly lower in Black patients (50.7 vs 73.5%; P<0.007). Secondary: There were no serious clinical or metabolic side effects reported, with the exception of pedal edema which occurred more frequently with amlodipine monotherapy.
Messerli et al.[94] (2000) <u>Study 1:</u> Amlodipine and benazepril 5-10 mg to 5-20 mg QD (fixed-dose combination	2 DB, MC, RCT Patients 18 to 80 years of age with uncomplicated essential HTN	N=1,079 8 weeks	Primary: Change in DBP from baseline Secondary: Change from baseline in SBP and heart rate	Primary: Study 1 Significant reductions in DBP were observed with benazepril and amlodipine 10-5 and 20-5 mg (-9.4 and -9.7 mm Hg, respectively) compared to nifedipine 30 mg (-7.0 mm Hg; P<0.05), but not nifedipine 60 mg (-8.5; P>0.05). Study 2 Benazepril and amlodipine 10-5 (-8.9 mm Hg) and 20-5 mg (-9.1 mm Hg)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
product) vs nifedipine 30 to 60 mg/day <u>Study 2:</u> Amlodipine and benazepril 5-10 mg to 5-20 mg QD (fixed-dose combination product) vs amlodipine 5 to 10 mg QD				produced significantly greater reductions in DBP than amlodipine 5 mg (-6.8 mm Hg; P<0.05), but not amlodipine 10 mg (-8.7 mm Hg; P>0.05). Secondary: Study 1 Significant reductions in SBP were observed with benazepril and amlodipine 20-5 mg (-11.6 mm Hg) compared to nifedipine 30 mg (-7.9 mm Hg; P<0.05). Significantly less edema was reported with combination therapies (3.1 to 3.8%; P≤0.001) compared to nifedipine 60 mg (15.5%; P=0.008) but not nifedipine 30 mg (5.4%). Study 2 Significant reductions in SBP were observed with benazepril and amlodipine 20-5 mg (-9.1 mm Hg) compared to amlodipine 5 mg (-5.3 mm Hg; P<0.05). There were no significant difference in SBP between amlodipine 10 mg and the combination therapies. Significantly less edema (P<0.001) was reported with amlodipine 5 mg (4.9%) and combination therapies (1.5 to 2.2%) compared to amlodipine 10 mg (23.6%).
Hilleman et al.[95] (1999) Benazepril and amlodipine (fixed-dose combination product) vs monotherapy (atenolol, HCTZ, captopril, enalapril,	MA Patients with mild-to-moderate essential HTN	82 trials ≥4 weeks	Primary: Absolute change in supine DBP from baseline Secondary: Percent of patients who achieved blood pressure control, safety	Primary: The mean absolute decrease in supine DBP ranged from 9.7 to 13.3 mm Hg with verapamil showing the greatest effect and captopril the least. When studies were weighted by sample size, amlodipine and benazepril, atenolol, lisinopril, and verapamil showed the greatest blood pressure effect. Secondary: The average percentage of patients defined as controlled after treatment varied from 53.5 to 79.0%, with amlodipine and benazepril (74.3%) and lisinopril (79.0%) showing the highest percentage control (P=0.096). The incidence of adverse events ranged from 12.1 to 41.8%, with lisinopril and verapamil showing the lowest incidences (12.1% and 14.1%, respectively) and nifedipine the highest incidence. Lisinopril demonstrated

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
lisinopril, amlodipine, diltiazem, nifedipine, verapamil)				significantly less overall side effects compared to nifedipine (P=0.030). Nifedipine demonstrated a higher withdrawal rate due to side effects compared to atenolol, HCTZ, enalapril, amlodipine, and diltiazem (P=0.002). Although amlodipine and benazepril had the lowest rate of withdrawals due to adverse events, lack of significant change was due to the low number of cohorts available for analysis.
Jamerson et al.[96] (2007) ACCOMPLISH Benazepril 20 to 40 mg QD and HCTZ 12.5 to 25 mg QD vs benazepril 20 to 40 mg QD and amlodipine 5 to 10 mg QD	DB, MC, RCT Patients >60 years of age with HTN and at high risk of cardiovascular events	N=10,704 Analysis performed at 6 months (complete trial duration 5 years)	Primary: Changes in mean SBP from baseline to 6 months, blood pressure control rates (SBP/DBP <140/90 mm Hg or <130/89 mm Hg for patients with diabetes and chronic kidney disease) Secondary: Not reported	Primary: At baseline, 97% of subjects were treated with antihypertensive medications at entry, but only 37% of participants had blood pressure control. Mean blood pressure fell from 145/80 to 132/74 mm Hg after six months of treatment with either combination regimen (P<0.001). The six month blood pressure control rate was 73% in the overall trial (78% in the United States), 43% in diabetics, and 40% in patients with renal disease. Of the patients uncontrolled, 61% were not on maximal medications. Secondary: Not reported
Kereiakes et al.[97] (2007) Benazepril 10 mg/day for 2 weeks, then 20 mg/day for 2 weeks, then benazepril 20 mg/day plus amlodipine 5 mg/day for 4 weeks, then benazepril 20 mg/day plus	DB, DD, MC, PG, RCT Patients with stage 2 HTN	N=190 12 weeks	Primary: Change in mean seated SBP at the end of week 12 Secondary: DBP at the end of week 12, percent of patients attaining blood pressure goals of <140/90, <130/85, and <130/80 mm Hg	Primary: Patients treated with olmesartan and HCTZ experienced significantly greater reductions in mean seated SBP at week 12 than patients treated with benazepril plus amlodipine (least square mean change, -32.5 vs -26.5 mm Hg; P=0.024; least square mean treatment difference, -6.0 mm Hg; 95% CI, -11.1 to -0.8). Secondary: The least square mean change for reduction in DBP approached statistical significance with olmesartan and HCTZ compared to benazepril plus amlodipine at week 12 (P=0.056). The percentage of patients achieving goal rates at the end of the study for olmesartan and HCTZ and benazepril plus amlodipine were 66.3 and 44.7% (P=0.006) for <140/90 mm Hg, 44.9 vs 21.2% (P=0.001) for

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
amlodipine 10 mg/day for 4 weeks vs olmesartan 20 mg/day for 2 weeks, then 40 mg/day for 2 weeks then olmesartan and HCTZ 40-12.5 mg/day for 4 weeks increased to 40-25 mg for 4 weeks				<130/85 mm Hg, and 32.6 and 14.1% (P=0.006) for <130/80 mm Hg. Both treatments were well tolerated.
Waeber et al.[98] (2001) Valsartan 80 mg QD, which was switched to valsartan 80 mg and HCTZ 12.5 mg QD or valsartan 80 mg and benazepril 10 mg QD	OL, RCT Patients with mild-to-moderate uncontrolled HTN (DBP ≥90) while on valsartan monotherapy	N=327 4 weeks	Primary: Efficacy and safety Secondary: Not reported	Primary: The two combinations produced an additional blood pressure reduction compared to monotherapy (P<0.001 for both), with similar DBP reductions reported for the two combination groups (-4.5 mm Hg with valsartan plus HCTZ and -3.3 mm Hg with valsartan plus benazepril). SBP reductions of -6.7 and -3.2 mm Hg with valsartan plus HCTZ and valsartan plus benazepril, respectively, were reported (P=0.1). At the end of the trial, the blood pressure of the responders to valsartan monotherapy was lower than that of patients requiring combination therapy. Valsartan given alone or in association with HCTZ or benazepril was well tolerated. Secondary: Not reported
Malacco et al.[99] (2002)	DB, MC, RCT	N=397	Primary: Reduction in	Primary: Significantly lower sitting DBP (-2.7 mm Hg; P<0.001) and SBP (-3.7 mm

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Captopril and HCTZ 50-25 mg/day (fixed-dose combination) vs amlodipine and benazepril 5-10 mg/day (fixed-dose combination)	Patients with mild-to-moderate arterial HTN (sitting DBP >95 mm Hg and/or SBP >160 mm Hg) inadequately controlled by monotherapy with an ACE inhibitor, calcium-channel blocking agent or diuretic	12 weeks	sitting DBP and SBP Secondary: Percentage of patients responding to therapy (DBP<90 mm Hg, reduction in DBP ≥10 mm Hg or SBP ≥20 mm Hg, or SBP <150 mm Hg)	Hg; P<0.001) were achieved with amlodipine and benazepril compared to captopril and HCTZ. Secondary: Significantly more amlodipine and benazepril patients responded to therapy (94.8%) compared to captopril and HCTZ (86.0%; P=0.004). No differences in adverse events were reported between the two treatment groups.
Elliot et al.[100] (1999) Enalapril 10 mg QD vs enalapril and felodipine ER 5-5 mg/day (fixed-dose combination) After 6 weeks, all patients received the fixed-dose combination for an additional 6 weeks.	DB, PG, PRO, RCT, XO Patients with sitting DBP >95 mm Hg and <115 mm Hg	N=217 12 weeks	Primary: Change in sitting DBP, proportion of responders (DBP <90 mm Hg or a reduction of >10 mm Hg) Secondary: Not reported	Primary: Patients receiving combination therapy had significantly greater reductions in sitting SBP and DBP compared to baseline (P<0.05 and P<0.01, respectively). More patients receiving combination therapy were classified as responders than patients receiving enalapril monotherapy (59 vs 41%; P<0.01). When patients originally taking 10 mg enalapril were crossed over to the combination therapy for an additional six weeks, there was a further blood pressure reduction and increase in response rate, with loss of significant differences compared to those treated continuously with the combination for the entire 12 weeks. There were no significant differences in tolerability between the regimens. Secondary: Not reported
Prisant et al.[101] (1995) Enalapril 5, 10, or	DB, MC, PG, RCT Patients ≥21 years with mild to	N=218 17 weeks	Primary: Mean change from baseline in SBP and DBP, lab	Primary: Mean decreases in SBP and DBP from baseline were 13.4/10.7 mm Hg for bisoprolol and HCTZ patients, 12.8/10.2 mm Hg for amlodipine patients, and 7.3/6.6 mm Hg for enalapril patients. The hypotensive effects were

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
20 mg vs bisoprolol and HCTZ 2.5-6.25, 5-6.25, or 10-6.25 mg/day (fixed-dose combination product) vs amlodipine 2.5, 5, or 10 mg	moderate essential HTN, (average sitting DBP 95 to 114 mm Hg) each treatment was once daily and titrated to effect		measurements, adverse events, QOL questionnaire Secondary: Not reported	significant for all three groups (P<0.001). SBP and DBP mean changes from baseline for the bisoprolol and HCTZ group and the amlodipine group were greater than the change from baseline for the enalapril group (P<0.01). Response rates (DBP ≤90 mm Hg or ≥10 mm Hg decrease from baseline) were 71% for the bisoprolol and HCTZ group, 69% for the amlodipine group, and 45% for the enalapril group. The response rates for the bisoprolol and HCTZ and the amlodipine groups differed significantly from the enalapril group (P<0.01). Twenty nine percent of bisoprolol patients had adverse experiences compared to 42% of amlodipine patients (P=0.12). Nearly 47% of enalapril patients had adverse experience compared to bisoprolol (P=0.04). Adverse events reported included headache, fatigue, peripheral edema, and dizziness. Drug related adverse events were 16% for the bisoprolol and HCTZ patients, 21% for the amlodipine patients, and 23% for the enalapril patients. There was no significant difference between the groups. Enalapril demonstrated a mean decrease from baseline of 7.9 mg/dL for TC (P=0.02 vs amlodipine) and 6.6 mg/dL for LDL-C (P=0.04 vs amlodipine) which were not significantly different from the increase from the bisoprolol and HCTZ group of 1.7 mg/dL (P=0.07 vs enalapril) for TC and +0.6 mg/dL in LDL-C. However, the increase in TGs was highest for bisoprolol and HCTZ-treated patients compared to amlodipine- and enalapril-treated patients (P=0.08, for bisoprolol and HCTZ vs enalapril). There was not a significant difference from baseline or between treatment groups in QOL scores: 0.9 for the bisoprolol and HCTZ group, 0.5 for the amlodipine group, and 2.3 for the enalapril group.
Ruilope et al.[102] (2001) Enalapril 5 mg	DB, MC, PG, RCT Patients greater than 65 years of age with	N=334 12 weeks	Primary: Mean change from baseline in sitting SBP	Primary: No significant difference between groups in change from baseline in sitting SBP was observed (P=0.76).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD (titration to 10 mg followed by 20 mg was allowed every 3 weeks) vs eprosartan 600 mg QD (titration to 800 mg QD was allowed after 3 weeks)	essential HTN, either newly diagnosed or for whom a change in existing antihypertensive medication is indicated due to poor control		Secondary: Normalization rate for sitting SBP and DBP, response rate for sitting SBP and DBP, mean change from baseline in DBP	Secondary: No significant difference between groups in change from baseline in sitting DBP was observed (P=0.84). BP response rates for SBP and DBP were significantly greater for eprosartan at week three (P≤0.033) but the significant difference had disappeared by endpoint (P≥0.49). Normalization rates for SBP were low in both groups (P value not reported). Normalization rates for DBP were higher in both groups than SBP normalization rates (P value not reported).
Karlberg et al.[103] (1999) TEES Enalapril 5 to 20 mg QD vs telmisartan 20 to 80 mg QD HCTZ 12.5 or 25 mg QD could be added to either group as needed to reach DBP goal (≤90 mm Hg).	DB, DD, MC, PG, RCT Patients ≥65 years of age with mild- to moderate HTN	N=278 26 weeks	Primary: Change from baseline in supine SBP and DBP Secondary: Proportion of responders, safety	Primary: Both treatments had similar rates of HCTZ use. Both treatments showed comparable decreases in blood pressure. Mean changes in DBP were -12.8 mm Hg for telmisartan and -11.4 mm Hg for enalapril (P=0.074). Mean changes in SBP were -22.1 mm Hg for telmisartan and -20.1 mm Hg for enalapril (P=0.350). Secondary: Overall, 63 and 62% of patients responded to telmisartan and enalapril, respectively, with a DBP of <90 mm Hg. Both regimens provided effective blood pressure lowering over the 24-hour dosing interval, as determined by ambulatory blood pressure monitoring. Both regimens were well tolerated; however, the enalapril group had a higher incidence of cough than the telmisartan group (15.8 vs 6.5%; P value reported).
Estacio et al.[104] (1998) ABCD Enalapril 5 to 40 mg/day	DB, PRO, RCT Patients between the ages of 40 and 74 years with NIDDM, baseline DBP ≥90	N=470 67 months	Primary: Effect of intensive (target DBP of 75 mm Hg) or moderate (target DBP between 80 to	Primary: Analysis of the 470 patients in the trial who had HTN (DBP ≥90 mm Hg) showed similar control of blood pressure, blood glucose and lipid concentrations between the two study medications throughout the five years of follow-up.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs nisoldipine 10 to 60 mg/day	mm Hg and receiving no antihypertensive medications at the time of randomization		89 mm Hg) blood pressure control on the incidence and progression of complications of diabetes; compare enalapril to nisoldipine as a first-line antihypertensive agent Secondary: Incidence of MI	Secondary: Nisoldipine was associated with a higher incidence of fatal and nonfatal MI than enalapril (RR, 7.0; 95% CI, 2.3 to 21.4).
Williams et al.[105] (2004) Enalapril 10 mg QD vs eplerenone 50 mg QD vs Both medications were titrated to 200 (eplerenone) or 40 (enalapril) mg/day if needed for optimal blood pressure control (DBP < 90 mm Hg).	AC, DB, MC, PG, RCT Patients ≥18 years of age with stage 1 to 2 HTN (seated DBP ≥90 but <110 mm Hg, with a seated SBP <190 mm Hg)	N=499 12 months	Primary: Change in seated trough DBP at 6 months Secondary: Change in seated trough SBP at 6 months, reduction in SBP and DBP at 12 months, reduction in urine albumin/ creatinine ratio, adverse events	Primary: At six months, both treatments exhibited comparable reductions in DBP from baseline (P=0.91). Secondary: At six months, both treatments exhibited comparable reductions in SBP from baseline (P=0.20). At 12 months, both treatments exhibited comparable reductions in SBP and DBP from baseline (P=0.25 and P=0.33). Eplerenone-treated patients exhibited a significant reduction from baseline in urine albumin/creatinine ratio compared to enalapril-treated patients (61.5 vs 25.7%; P=0.01). There were no significant differences in overall treatment-emergent adverse events between the two treatments (P value not reported). There were no sex hormone related adverse events in eplerenone-treated patients. There were no clinically significant differences between the two treatments in any of the laboratory tests assessed. There were two eplerenone- and enalapril-treated patients that experienced hyperkalemia of ≥5.5 mmol/L.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tatti et al.[106] (1998) FACET Fosinopril 20 mg QD vs amlodipine 10 mg QD If blood pressure was not controlled on monotherapy, the other study drug was added.	OL, PRO, RCT Men and women, diagnosed with HTN (SBP >140 mm Hg or DBP >90 mm Hg) and non-insulin dependent diabetes	N=380 Up to 3.5 years	Primary: Blood pressure Secondary: Fasting serum glucose, serum creatinine, plasma insulin, HbA_{1c}, TC, HDL-C, TG, fibrinogen, microalbuminuria	Primary: Both treatment groups significantly lowered SBP and DBP from baseline (P<0.05). SBP was lower in the amlodipine group by 4 mm Hg than in the fosinopril group (P<0.01). There was no difference in DBP, both groups decreased by 8 mm Hg. Amlodipine was added by 30.7% of the fosinopril group and fosinopril was added by 26.2% of the amlodipine group (P>0.1). Secondary: No difference between the groups was found for serum creatinine, HbA_{1c}, and triglycerides at the endpoint (P>0.05). Fasting serum glucose, serum insulin and microalbuminuria were significantly lower at endpoint for both groups but not significantly different from each other (P>0.05). Total cholesterol increased in both groups, and high-density lipoprotein cholesterol increased significantly in the fosinopril group (P<0.05). No difference in fibrinogen levels was observed between the groups at the end of the trial (P>0.05).
Whelton et al.[107] (1990) Lisinopril 10 to 40 mg QD vs captopril 25 to 100 mg BID Doses were titrated until	DB, MC, PG, RCT Patients with mild-to-moderate essential HTN	N=70 Up to 8 weeks	Primary: Reduction in blood pressure in both ambulatory and office settings Secondary: Not reported	Primary: Lisinopril-treated patients showed significantly greater reductions in SBP and DBP measured by 24-hour ambulatory blood pressure monitoring compared to captopril-treated patients (P=0.023 and P=0.007, respectively). Greater reductions (P<0.05) were also noted in patients receiving lisinopril at hours 10 to 12, suggesting two blood pressure troughs for those receiving captopril. The difference in mean reductions between treatment groups from baseline to the final visit approached statistical significance for office SBP (P=0.06) and DBP (P=0.09) in favor of patients receiving lisinopril. Both drugs were well tolerated, and no patients withdrew from either

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
patients responded to treatment (defined by a decrease in office DBP to <90 mm Hg or ≥10 mm Hg decrease from baseline).				treatment group. Secondary: Not reported
Strasser et al.[108] (2007) Lisinopril 20 to 40 mg QD vs aliskiren 150 to 300 mg QD HCTZ may be added if additional blood pressure control was required.	AC, DB, DD, MC, PG, RCT Men and women with uncomplicated severe HTN (mean sitting DBP 105 to 119 mm Hg)	N=183 8 weeks	Primary: Safety Secondary: Change in mean sitting DBP and SBP, percentage of responders	Primary: Both active treatments were well tolerated with an incidence of adverse events of 32.8% for aliskiren and 29.3% for lisinopril. The proportion of patients discontinuing treatment due to adverse events was 3.2% for aliskiren and 3.4% for lisinopril. The most frequently reported adverse events in both groups were headache, nasopharyngitis and dizziness. Secondary: Aliskiren showed similar reductions from baseline to lisinopril in mean sitting DBP (-18.5 vs -20.1 mm Hg) and SBP (-20.0 and -22.3 mm Hg). Responder rates were 81.5% with aliskiren and 87.9% with lisinopril. Approximately half of patients required the addition of HCTZ to achieve blood pressure control (53.6% for aliskiren and 44.8% for lisinopril).
Rosei et al.[109] (2003) Lisinopril 20 mg QD vs nebivolol 5 mg QD	DB, MC, PG, RCT Patients between 24 and 65 years with mild to moderate uncomplicated essential HTN that was newly diagnosed, or previous antihypertensive therapy was withdrawn at >1	N=65 12 weeks	Primary: Response rates, changes in sitting blood pressure Secondary: Standing blood pressure, sitting and standing heart rate	Primary: There was not a significant difference in response rates observed between the two treatment groups. Both treatment groups significantly reduced sitting SBP (P<0.0001) and DBP (P<0.0001) throughout the study compared to baseline but there were no significant differences observed between the treatment groups at most visits, but at week eight, DBP was significantly lower in the nebivolol group compared to the lisinopril group (P<0.05). Secondary: There was not a significant difference observed between treatment groups in standing blood pressure measurements.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	month before active treatment, and had a sitting DBP of >95 and <114 mm Hg			Both treatment groups significantly reduced sitting heart rate (P<0.01) throughout the study compared to baseline but there were no significant differences observed between the treatment groups at most visits, but at week eight, heart rate were significantly lower in the nebivolol group compared to the lisinopril group (P<0.05).
Wald et al.[110] (2008) Lisinopril 5mg QD vs atenolol 25 mg QD vs lisinopril 5 mg and atenolol 25 mg QD vs placebo	DB, DD, RCT, XO Patients ≥ 40 years enrolled in a HTN or anticoagulation clinic	N=47 16 weeks	Primary: Reduction in blood pressure Secondary: Not reported	Primary: The mean reductions in SBP in the atenolol alone, lisinopril alone and atenolol plus lisinopril groups were 16.1, 12.5, and 22.9 mm Hg, respectively. The mean reductions in DBP in the atenolol alone, lisinopril alone and atenolol plus lisinopril groups were 9.8, 6.8, and 13.9 mm Hg, respectively. The reductions with lisinopril plus atenolol group were significantly higher than either agent as monotherapy (P<0.001). Secondary: Not reported
Karotsis et al.[111] (2006) Lisinopril 10 mg QD vs chlorthalidone 12.5 mg QD	RCT Patients 25 to 79 years of age with uncontrolled HTN (average office blood pressure >140/90 mm Hg for all or >153/85 mm Hg for diabetics or patients <65 years of	N=211 8 weeks	Primary: Blood pressure Secondary: Not reported	Primary: There was a significant decline in both office and home SBP and DBP during the trial with all treatments. The antihypertensive effect was more pronounced and reached significance when home blood pressure monitoring was used in comparison to office blood pressure without the white-coat effect (P<0.001 for all blood pressure changes). With or without the white-coat effect, blood pressure still declined and the differences were significant (P<0.0001 for all blood pressure changes). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs felodipine 5 mg QD vs valsartan 80 mg QD All patients also received diltiazem 240 mg QD.	age, confirmed on 2 office visits ≥1 week apart) after ≥4 weeks of OL monotherapy with diltiazem at 240 mg QD			
McInnes et al.[112] (2000) Lisinopril and HCTZ 10-12.5 mg/day (fixed-dose combination product) vs candesartan and HCTZ 8-12.5 mg/day (fixed-dose combination product)	DB, DD, MC, PG, RCT Patients 20 to 80 years of age with mild-to-moderate HTN on prior antihypertensive monotherapy	N=355 26 weeks	Primary: Mean changes in DBP Secondary: Mean changes in SBP and heart rate, proportion of responders and controlled patients, safety	Primary: Changes in mean sitting DBP did not differ significantly between the groups (mean difference, 0.5 mm Hg; P=0.20). Secondary: No significant differences between the groups were reported for mean sitting SBP, heart rate, proportion of responders and controlled patients. Both regimens were well tolerated but a greater percentage of those in the lisinopril based group (80 vs 69%) had a least one side effect (P=0.020). The proportion of patients spontaneously reporting cough (23.1 vs 4.6%) and discontinuing therapy due to adverse events (12.0 vs 5.9%) was also higher in the lisinopril based group compared to the candesartan based group.
Poldermans et al.[113] (2007) Lisinopril 10 to 20 mg QD and HCTZ 12.5 mg QD	AC, DB, MC, PG, RCT Males and females, ages 18 years and older with HTN (mean DBP ≥110 mm Hg and <120	N=130 6 weeks	Primary: Safety/adverse events, vital signs, hematology, biochemistry variables Secondary:	Primary: Both treatments were well tolerated, 26 (40.6%) of patients receiving amlodipine and valsartan and 21 (31.8%) of patients receiving lisinopril and HCTZ reported an adverse events and most were not considered drug related. Peripheral edema was reported more often in the amlodipine and valsartan group than the lisinopril and HCTZ group (7.7 vs 1.5%) and cough was

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs amlodipine 5 to 10 mg QD and valsartan 160 mg QD	mm Hg)		Efficacy (mean DBP, response rate, proportion of patients with mean DBP <90 mm Hg or a ≥10 mm Hg reduction from baseline)	reported less often in the amlodipine and valsartan group than the receiving lisinopril and hydrochlorothiazide group (1.6 vs 3.0%). No difference was found between the treatments in changes in laboratory values or biochemistry variables. Secondary: Both treatments led to a reduction in mean SBP and DBP (P<0.0001 for both from baseline) but were not significantly different from each other. Mean blood pressure for each group at study end: amlodipine and valsartan 135.0/83.6 mm Hg and lisinopril and HCTZ 138.7/85.2 mm Hg. The response rate was similar among the groups (100 vs 95.5%; P value not significant).
Duprez et al.[114] (2010) AGELESS Aliskiren 150 to 300 mg QD vs ramipril 5 to 10 mg QD The addition of HCTZ was allowed at week 12 and amlodipine was allowed at week 22 in patients not achieving adequate blood pressure control.	AC, DB, MC, RCT Patients ≥65 years of age with essential HTN (mean sitting SBP ≥140 and <180 mm Hg and mean sitting DBP <110mm Hg)	N=901 36 weeks	Primary: Change in mean seated SBP at week 12 Secondary: Change in mean sitting SBP at week 36, change in mean sitting DBP at week 12 and week 36, percentage of patients who achieved blood pressure control (mean sitting SBP/DBP <140/90 mm Hg in non-diabetic patients and <130/80 mm Hg in diabetic patients)	Primary: At week 12, aliskiren lowered mean sitting SBP by 14 mm Hg and ramipril decreased mean sitting SBP by 11.6 mm Hg (difference, -2.3 mm Hg; 95% CI, -4.3 to -0.3). Aliskiren monotherapy showed statistically non-inferior (P<0.001) and statistically superior (P=0.02) reductions in mean sitting SBP compared with ramipril monotherapy. Secondary: At week 22, aliskiren decreased mean sitting SBP by 19.6 mm Hg and ramipril decreased mean sitting SBP by 17 mm Hg (difference, -2.4 mm Hg; 95% CI, -4.5 to -0.3; P=0.03). At week 36, aliskiren decreased mean sitting SBP by 20 mm Hg and ramipril decreased mean sitting SBP by 18.1 mm Hg (difference, -1.9 mm Hg; 95% CI, -4.0 to 0.2; P=0.07). At week 12, aliskiren decreased mean sitting DBP by 5.1 mm Hg and ramipril decreased mean sitting DBP by 3.6 mm Hg (difference, -1.5 mm Hg; 95% CI, -2.6 to -0.5; P<0.01). At week 22, aliskiren decreased mean sitting DBP by 8.2 mm Hg and ramipril decreased mean sitting DBP by 7.3 mm Hg (difference, -0.8 mm Hg; 95% CI, -2.0 to 0.3; P=0.14).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			at week 12 and week 36, percentage of patients who required add-on therapy	At week 36, aliskiren decreased mean sitting DBP by 8.2 mm Hg and ramipril decreased mean sitting DBP by 7.0 mm Hg (difference, -1.2 mm Hg; 95% CI, -2.3 to -0.1; P=0.03). The percentage of patients achieving blood pressure control was significantly greater with aliskiren (42%) compared to ramipril (33%) at week 12 (P<0.01). At week 22, a significantly greater proportion of patients achieved blood pressure control with aliskiren (62%) compared to ramipril (50%; P<0.001). At week 36, similar blood pressure control rates were achieved with aliskiren (59%) and ramipril (51%; P=0.01). By week 36, a significantly greater percentage of patients receiving ramipril compared to aliskiren required additional HCTZ (56 vs 46%; P<0.01). By week 36, a greater percentage of patients receiving ramipril (16%) compared to aliskiren (12%) required add-on therapy with both HCTZ and amlodipine (P=0.048). More patients receiving aliskiren were receiving monotherapy (42%) than patients receiving ramipril (29%) at week 36.
Anderson et al.[115] (2008) Aliskiren 150 to 300 mg QD vs ramipril 5 to 10 mg QD The addition of HCTZ was allowed in patients not	AC, DB, MC, PC, RCT Men and women ≥18 years with essential HTN (mean sitting DBP 90 to 109 mm Hg)	N=842 26 weeks	Primary: Change in mean sitting DBP at week 26 Secondary: Change in mean sitting SBP at week 26, change in mean sitting SBP and DBP at week 6 and 12 (comparing aliskiren and ramipril monotherapy),	Primary: Reductions in mean sitting DBP at week 26 were significantly greater with aliskiren-based therapies (-13.2 mm Hg) compared to ramipril-based therapies (-12.0 mm Hg; P=0.0250). Secondary: Reductions in mean sitting SBP at week 26 were significantly greater with aliskiren-based therapies (-17.9 mm Hg) compared to ramipril-based therapies (-15.2 mm Hg; P=0.0036). Mean changes in sitting SBP were significantly greater with aliskiren (-12.9 and -14.0 mm Hg, respectively) compared to ramipril (-10.5 and -11.3, respectively) at weeks six and 12 (P=0.0041 and P=0.0027, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
achieving adequate blood pressure control. The study did not specifically analyze the effects of HCTZ on either treatment regimen.			proportion achieving blood pressure control (<140/90 mm Hg), proportion achieving SBP control (<140 mm Hg), safety	Mean changes in sitting DBP were not significantly greater with aliskiren (-10.5 and -11.3 mm Hg, respectively) compared to ramipril (-9.5 and -9.7, respectively) at week six, but were significantly greater at week 12 (P=0.0689 and P=0.0056, respectively). The proportion of patients achieving overall blood pressure control (<140/90 mm Hg) was significantly higher with aliskiren-based therapy (61.4%) compared to ramipril-based therapy (53.1%; P=0.0205) at week 26. Also, the proportion of patients achieving SBP control (<140 mm Hg) was significantly higher with aliskiren-based therapy (72.5%) compared to ramipril-based therapy (64.1%; P=0.0075) at week 26. The majority of adverse events reported during the active treatment period were mild or moderate in intensity and transient. Most events occurred at a similar incidence in the two groups with the exception of cough which was considered treatment-related in 5.5% of patients receiving ramipril vs 2.1% of patients receiving aliskiren.
Miranda et al.[116] (2008) Ramipril 2.5 to 10 mg QD and amlodipine 2.5 to 10 mg QD vs amlodipine 2.5 to 10 mg QD	AC, DB, MC, RCT Adults 40 to 79 years of age with stage 1 or 2 essential HTN	N=222 18 weeks	Primary: Change in SBP and DBP Secondary: Safety and tolerability	Primary: The mean changes in ambulatory BP were greater with amlodipine and ramipril compared to amlodipine monotherapy (SBP, -20.21 vs -15.31 mm Hg and DBP, -11.61 vs -8.42 mm Hg, respectively; both, P=0.002]. There was no significant difference among the treatment groups in office BP (SBP, -26.60 vs -22.97 mm Hg and DBP, -16.48 vs -14.48 mm Hg; both, P value not significant). Secondary: Twenty-nine patients (22.1%) treated with combination therapy and 41 patients (30.6%) treated with monotherapy experienced ≥1 adverse event considered possibly related to study drug. The combination-therapy group had lower prevalence of edema (7.6 vs 18.7%; P=0.011) and a similar prevalence of dry cough (3.8 vs 0.8%; P value not significant).
Bönner et al.[117] (2013) Azilsartan (AZL) 20mg titrated to 40 mg	DB, RCT Patients ≥18 years of age with clinic systolic blood pressure (SBP) 150	N=884 24 weeks	Primary: Change in trough, seated clinic SBP Secondary: Change from	Primary: After 24 weeks of treatment, trough, sitting, clinic SBP decreased significantly in all the groups. The changes from baseline were significantly greater for the AZL 40 and 80 mg treatment groups (−20.6±0.95 and −21.2±0.95 mm Hg, respectively) than for RAM 10 mg (−12.2±0.95 mm Hg). The differences between the AZL-treated subjects

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs azilsartan (AZL) 20mg titrated to 80 mg vs ramipril (RAM) 2.5 mg titrated to 10 mg	to 180 mm Hg		baseline to week 24 in trough, seated clinic DBP, measures of ambulatory BP, and BP response rates	and the RAM-treated subjects were −8.4 mm Hg for AZL 40 and −9.0 mm Hg for AZL 80 (P<0.001 for both comparisons). Secondary: Change in trough, sitting, DBP was −10.2±0.55 mm Hg in the AZL 40 mg group, −10.5±0.55 mm Hg in the AZL 80 mg and −4.9±0.56 mm Hg in the RAM 10 mg group. AZL 40 and 80 mg reduced ambulatory SBP and DBP significantly more than RAM for all ABPM time intervals evaluated, including 24-hour mean, mean daytime, mean nighttime and mean trough pressure. The differences between the AZL and RAM groups proportion of subjects achieving SBP and DBP response criteria were highly significant (P<0.001). More subjects achieved a reduction in clinic BP to <140/90 mm Hg and/or a reduction in BP≥20/10 mm Hg at week 24 following treatment with AZL compared with RAM (54.0% and 53.6% for AZL 40 and 80 mg vs 33.8% with RAM 10 mg, respectively; P<0.001).
Williams et al.[118] (2009) PRISMA I and PRISMA II Ramipril 2.5 mg QD for 2 weeks then force titration to 5 mg QD for 6 weeks then 10 mg QD for 6 weeks vs telmisartan 40 mg QD for 2 weeks then force titration to 80 mg QD for 12 weeks	Pooled analysis: blinded endpoint, OL, PRO, RCT Patients ≥18 years of age with mild- to moderate HTN	N=1,613 14 weeks	Primary: Change from baseline in mean ambulatory BP during the final 6 hours of the 24-hour dosing interval Secondary: Change from baseline in mean ambulatory blood pressure during the 24-hour dosing interval, morning, daytime and nighttime ambulatory blood	Primary: A significantly greater reduction in mean ambulatory blood pressure during the last six hours of the 24-hour dosing interval was observed with telmisartan 80 mg group compared to ramipril 5 and 10 mg (P<0.0001). Secondary: Significantly greater reductions in mean 24-hour, morning, daytime, nighttime and 24-hour blood pressure load were observed with telmisartan 80 mg compared to ramipril 5 and 10 mg (P<0.0001). Significantly greater reductions in treatment response and blood pressure control rates were observed with telmisartan 80 mg compared to ramipril 5 and 10 mg (P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			pressure, 24-hour blood pressure load, treatment response, blood pressure control	
O'Brien et al.[119] (2007) Aliskiren 150 mg QD for 3 weeks, then HCTZ 25 mg QD was added for an additional 3 weeks (if ABPM remained ≥135/85 mm Hg) vs irbesartan 150 mg QD for 3 weeks, then aliskiren 75 mg QD added for 3 weeks, then aliskiren 150 mg QD added for 3 weeks vs ramipril 5 mg QD for 3 weeks, then aliskiren 75 mg QD added for 3 weeks, then aliskiren 150 mg QD added for 3	3 OL studies Men and women 18 to 80 years with ambulatory SBP ≥140 and ≤180 mm Hg without treatment	N=67 6 to 9 weeks	Primary: Change in daytime systolic ABPM with combination therapy compared with monotherapy Secondary: Change in daytime diastolic ABPM, nighttime systolic and diastolic ABPM, daytime and nighttime heart rates, plasma renin activity	Primary: Aliskiren coadministered with HCTZ (P=0.0007) or ramipril (P=0.03) led to significantly greater reductions in daytime systolic ABPM compared to monotherapy. There was a trend for a reduction in daytime systolic ABPM with the addition of aliskiren to irbesartan; however, this trend was not statistically significant. Secondary: Aliskiren plus HCTZ significantly lowered daytime diastolic ABPM compared to aliskiren monotherapy (P=0.0006). Changes in nighttime systolic and diastolic ABPM followed similar trends but did not achieve statistical significance (P=0.06 and P=0.09, respectively). No changes in heart rate were observed with either aliskiren regimen. Aliskiren added to irbesartan did not significantly change diastolic ABPM compared to irbesartan monotherapy; however, nighttime systolic and diastolic ABPM were significantly reduced (P<0.05 for all). No changes in heart rate were observed with either irbesartan regimen. Mean diastolic ABPM was significantly decreased with the addition of aliskiren 150 mg (P<0.05) but not aliskiren 75 mg to ramipril monotherapy. Both aliskiren doses significantly decreased nighttime systolic and diastolic ABPM (P<0.05 for all). No changes in heart rate were observed with either ramipril regimen. Aliskiren alone significantly inhibited plasma renin activity by 65% (P<0.0001), while ramipril and irbesartan monotherapy increased renin activity by 90 and 175%, respectively. When aliskiren was coadministered with HCTZ, ramipril or irbesartan, plasma renin activity remained similar to baseline levels or decreased.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
weeks				
Tytus et al.[120] (2007) Trandolapril 1 to 4 mg/day At 14 weeks after treatment initiation, subjects not achieving blood pressure targets could receive a combination of trandolapril 4 mg/day plus verapamil 240 mg/day with or without a diuretic.	MC, OL, PRO Patients with stage 1 or 2 HTN who were treatment naïve (82%) or uncontrolled on a diuretic (11%) or calcium-channel blocker (7%); uncontrolled HTN was defined as ≥140/90 mm Hg in subjects with no other risk factors or ≥130/80 mm Hg in subjects with diabetes or kidney disease	N=1,683 26 weeks	Primary: Percentage of patients reaching target blood pressure at 14 weeks Secondary: Percentages of subjects with stage 1 and 2 HTN who achieved target blood pressure, percentages of subjects who achieved a drop in SBP of ≥20 mm Hg and/or DBP ≥10 mm Hg, absolute changes in SBP and DBP, adverse events	Primary: At 14 weeks of treatment, 71.2% of patients who were treated with trandolapril monotherapy reached SBP/DBP <140/90 mm Hg. Secondary: At 26 weeks, 73.4% of patients achieved a target level of SBP/DBP <140/90 mm Hg. Of the 683 subjects with stage 2 HTN, 64.6% achieved the target level after 14 weeks of trandolapril and 67.9% after 26 weeks. At 14 weeks, 78.8% of subjects treated with a trandolapril regimen experienced a decrease in SBP of ≥20 mm Hg or a decrease in DBP of ≥10 mm Hg. Statistically significant (P<0.001) and clinically relevant mean decreases in SBP of -16.1 mm Hg and in DBP of -8.8 mm Hg were observed from four weeks of treatment onward for the overall study population. The mean reductions in SBP and DBP were -21.5 and -11.9 mm Hg, respectively at 14 weeks (P<0.001), and -22.4 and -12.7 mm Hg, respectively, at 26 weeks (P<0.001). A total of 343 predominantly mild, nonserious adverse events were attributed to the study drugs, reported by 15.3% of the 1,650 subjects. The most frequently reported nonserious adverse events were cough (6.3%); gastrointestinal disorders (2.3%), predominantly nausea; and headache (2.1%). No serious adverse events were attributed to the study treatment.
Tytus et al.[121] (2011) MAVIKtory Trandolapril 1 to 2 mg/day With or without existing antihypertensive therapy.	MC, OS Patients with HTN	N=8,787 6 months	Primary: Proportion of patients reaching blood pressure targets, safety Secondary: Not reported	Primary: The target of <140/90 mm Hg was achieved by 67.3% of patients. The lower mean target of 133.4/83.3 mm Hg for nondiabetic patients and 128.6/79.3 mm Hg for diabetic patients were achieved by 52.2%. Mean reductions from baseline to trial end were 19.4 mm Hg (95% CI, -19.9 to -19.0) in SBP and 10.1 mm Hg (95% CI, -10.4 to -9.8) in DBP. Cough was the most commonly reported adverse event (4.2%). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Pauly et al.[122] (1994) Trandolapril 4 mg QD vs captopril 50 mg BID If blood pressure was not normalized at 8 weeks, HCTZ 25 mg was added.	DB, MC, RCT Patients between 21 to 65 years with mild-to-moderate essential HTN (DBP of 95 to 115 mm Hg)	N=180 16 weeks	Primary: Morning pre-dosing supine DBP at 8 weeks of monotherapy Secondary: Supine SBP at 8 weeks of monotherapy, blood pressure at 16 weeks of therapy (including 8 weeks of monotherapy and 8 weeks of combination therapy with HCTZ)	Primary: Significantly greater mean reductions in supine DBP in the trandolapril group vs captopril group were observed after eight weeks of monotherapy (-13.5 vs -10.1 mm Hg; P=0.007). Secondary: Differences in supine SBP between treatment groups approached significance after eight weeks of monotherapy (P=0.06). Both SBP and DBP were significantly reduced at all time points compared to baseline for both treatment groups at the end of the study (P<0.05). The proportion of patients whose blood pressure normalized (supine and standing blood pressure ≤160/90 mm Hg) at the end of the study was 61% for trandolapril and 44% for captopril (P=0.02). The overall proportion of responders (DBP fell by ≥10 or to <90 mm Hg) was significantly greater in the trandolapril group (77%) than in the captopril group (58%; P<0.007).
Vaur et al.[123] (1995) Trandolapril 2 mg QD in the morning vs enalapril 20 mg QD in the morning	DB, RCT Patients between 18 to 70 years with mild-to-moderate primary HTN	N=88 3 weeks	Primary: 24-hour ambulatory SBP and DBP over an active 24-hour period and subsequent 24-hour period (to mimic a missed dose) Secondary: Not reported	Primary: Both trandolapril and enalapril showed similar reductions in SBP and DBP over the 24-hour period. In the trandolapril group, SBP and DBP decreased from 148/92 to 135/83 mm Hg (P<0.001). In the enalapril group, SBP and DBP decreased from 143/91 to 133/83 mm Hg (P<0.001). The trough/peak ratio on active treatment was 90% (SBP) and 54% (DBP) in the trandolapril group and 49% (SBP and DBP) in the enalapril group. Following the missed dose, trough/peak ratio decreased to 58% (SBP)/36% (DBP) for trandolapril and 10% (SBP)/19% (DBP) for enalapril. The blood pressure control was better sustained with trandolapril, such that significant falls in blood pressure were observed during the daytime, nighttime and early morning periods after a missed dose, whereas during the same periods, enalapril only significantly reduced blood pressure in the daytime period. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Karlberg et al.[124] (2000) Trandolapril 2 mg/day vs verapamil 240 mg/day vs trandolapril and verapamil 2-180 mg/day (fixed-dose combination)	DB, MC, PRO, RCT, XO Patients with uncomplicated primary HTN (sitting DBP between 95 and 115 mm Hg) between the ages of 20 to 80 years	N=226 2 months	Primary: Change in blood pressure and rate pressure product Secondary: Predictive value of plasma concentrations of active renin regarding the blood pressure response to the different treatment regimens, safety	Primary: The mean fall in blood pressure was significantly greater with the combination (20/15 mm Hg; P<0.00054), as compared to trandolapril (14/11 mm Hg) or verapamil (13/11) mm Hg. The difference between verapamil and trandolapril was not significant. Rate pressure product decreased significantly more on the combination (P<0.001) than on trandolapril or verapamil alone. Secondary: There was a significant positive correlation between blood pressure fall and plasma concentrations of active renin (e.g., the higher the initial active renin, the better the blood pressure response to trandolapril [P<0.045 for SBP and P<0.004 for DBP]). No relationships were found for either verapamil or the combination. All treatments were well tolerated and safe.
Pepine et al.[125] (2006) INVEST Verapamil SR (step 1), then add trandolapril if needed (step 2), then increase doses of both (step 3), then add HCTZ (step 4) (calcium antagonist strategy) vs atenolol (step 1), then add HCTZ if	Post hoc analysis of INVEST Patients with essential HTN	N=22,576 24 months	Primary: Risk for adverse outcome associated with baseline factors, follow-up blood pressure and drug treatments Secondary: Not reported	Primary: Previous heart failure (adjusted HR, 1.96), as well as diabetes (HR, 1.77), increased age (HR, 1.63), United States residency (HR, 1.61), renal impairment (HR, 1.50), stroke/TIA (HR, 1.43), smoking (HR, 1.41), MI (HR, 1.34), PVD (HR, 1.27), and revascularization (HR, 1.15) predicted increased risk. Follow-up SBP <140 mm Hg (HR, 0.82) or DBP <90 mm Hg (HR, 0.70) and trandolapril with verapamil SR (HR, 0.78 and 0.79) were associated with reduced risk. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
needed (step 2), then increase doses of both (step 3), then add trandolapril (step 4) (non-calcium antagonist strategy)				
Brunner et al.[126] (2007) INVEST Verapamil SR 240 mg and trandolapril 1 to 4 mg	Post hoc analysis of INVEST Patients with essential HTN	N=1,832 24 months	Primary: Factors influencing blood pressure response to trandolapril add-on therapy Secondary: Not reported	Primary: Trandolapril decreased mean unadjusted SBP and DBP by -9.1 and -4.1 mm Hg, respectively. The percentage of patients with blood pressure under control (<140/90 mm Hg) increased from 6.7 to 41.3% (P<0.0001). Adjusted blood pressure response was significantly associated with age and baseline SBP and DBP (P<0.0001). Whereas the decrease in SBP was more pronounced in younger patients, the opposite was observed for DBP decrease. DBP response was significantly associated with race. Specifically, the adjusted DBP decrease was significantly smaller in Hispanics and African Americans than whites (P=0.0032 and P=0.0069, respectively). However, Hispanics achieved a decrease in SBP and an increase in blood pressure control similar to the other ethnic groups. Secondary: Not reported
Cifkova et al.[127] (2000) Verapamil and trandolapril 180-2 mg QD (fixed-dose combination) (VT) vs	AC, OL, RCT, XO Caucasian patients aged 18 to 75 years with mild-to-moderate essential HTN (SBP 140 to 209 mm Hg and DBP 90 to 119 mm Hg)	N=100 8 months	Primary: LDL-C Secondary: Other lipid parameters (HDL-C, TC, TG, apolipoproteins AI and B, lipoprotein(a)), blood pressure	Primary: LDL-C was not significantly different between the two treatment groups (P=0.909). Secondary: All secondary lipid parameters remained unaltered except for HDL-C which was significantly higher with VT (1.39 vs 1.35 mmol/L; P<0.03). Serum potassium declined while uric acid and glucose increased on CH (P<0.001 for all).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
captopril and HCTZ 50-25 mg QD (fixed-dose combination) (CH) After 16 weeks, patients were switched to the other fixed combination for an additional 16 weeks.			parameters	While there were no significant differences with respect to adjusted mean DBP, adjusted mean SBP was slightly higher on treatment with VT than with CH. These differences reached statistical significance for the 24-hour and night-time means, although the absolute adjusted mean treatment differences were only 2.3 mm Hg (P=0.02) and 3.5 mm Hg (P=0.01), respectively. The number of patients who achieved DBP <90 mm Hg at the end of each treatment did not differ (56% VT vs 46% CH; P value not significant). Heart rate was significantly lower in the VT group than the CH group (treatment differences ranged from 2.8 to 4.5 bpm; P≤0.001 for all).
de Leeuw et al.[128] (1997) Verapamil SR and trandolapril 180-2 mg/day, atenolol and chlorthalidone 100-25 mg/day, or lisinopril and HCTZ 20-12.5 mg/day (fixed-dose combination products) vs placebo All patients entered a SB, placebo 4 week run in period.	DB, MC, PC, RCT Patients 18 to 70 years of age with essential HTN (WHO I or II) newly or unsuccessfully treated, with supine DBP 101 to 114 mm Hg in week 4 of the run in period	N=205 12 weeks	Primary: Changes in supine blood pressure, standing blood pressure response rates, normalization rates Secondary: Not reported	Primary: Each of the three treatments was significantly more effective than placebo in reducing seated DBP. Changes in DBP were as follows: verapamil SR and trandolapril, -13 (95% CI, -16 to -9); atenolol and chlorthalidone, -13 (95% CI, -16 to -9); lisinopril and HCTZ, -12 (95% CI, -15 to -9) and placebo, -3 (95% CI, -7 to 0) (P=0.0001 for all vs placebo), but there was not a significance among the treatments (P values not reported). Each of the three treatments was significantly more effective than placebo in reducing seated SBP. Changes in SBP were as follows: verapamil SR and trandolapril, -27 (95% CI, -33 to -21); atenolol and chlorthalidone, -28 (95% CI, -34 to -22); lisinopril and HCTZ, -23 (95% CI, -29 to -17) and placebo, -3 (95% CI, -9 to 3) (P=0.0001 for all vs placebo), but there was not a significance among the treatments (P values not reported). Effects on standing blood pressure demonstrated similar results as the effects on sitting blood pressure (P values not reported). Normalization of DBP (<90 mm Hg), corrected for placebo, were significantly higher with all treatments compared to placebo (verapamil SR and trandolapril, 33% [95% CI, 16 to 50; P<0.0005]; atenolol and chlorthalidone, 31% [95% CI, 14 to 48; P<0.002] and lisinopril and HCTZ, 25% [95% CI, 9 to 42; P<0.005]).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Response rates (normalization of DBP or a reduction in DBP >10 mm Hg), corrected for placebo, were significantly higher with all treatments compared to placebo (verapamil SR and trandolapril, 40% [95% CI, 22 to 58; P<0.0001], atenolol and chlorthalidone, 44% [95% CI, 27 to 61; P<0.0001] and lisinopril and HCTZ, 37% [95% CI, 19 to 55; P<0.0002]). Secondary: Not reported
Stanton et al.[129] (2010) Aliskiren 300 mg QD vs irbesartan, losartan, valsartan, ramipril, HCTZ, placebo	MA Adults with mild to moderate essential HTN	N=4,877 (8 trials) 4 to 12 weeks	Primary: Paradoxical blood pressure rises, as well as the percentage of patients with SBP increases (>10 or >20 mm Hg) or DBP increases (>5 or >10 mm Hg) from baseline Secondary: Not reported	Primary: There were no significant differences among the pooled aliskiren, irbesartan, losartan, valsartan, ramipril, and HCTZ groups in the incidence of SBP increases >10 mm Hg (P=0.30) and >20 mm Hg (P=0.28) or DBP increases >5 mm Hg (P=0.65) and >10 mm Hg (P=0.5). Increases in SBP and DBP occurred significantly more frequently in the pooled placebo group than the aliskiren group (P<0.001). Secondary: Not reported
Sundström et al.[130] (2023) Amlodipine 10 mg vs candesartan 16 mg vs lisinopril 20 mg vs	DB, PRO, XO, RCT Patients aged 40 to 75 years previously diagnosed with HTN, with SBP 140 to 159 mmHg within a five-year period prior to the start of the trial and SBP 140 to 179 mm Hg and DBP ≤109 mm Hg at the randomization visit	N=280 Six treatment periods, each being 7 to 9 weeks in duration, after a 2 week washout period; 1-week washout periods between each treatment period	Primary: Ambulatory daytime SBP at the end of each treatment period Secondary: Not reported	Primary: Participants had higher BP when taking HCTZ than when taking other treatments, when taking amlodipine compared with lisinopril, and when taking candesartan compared with lisinopril The blood pressure response to different treatments varied considerably between individuals (P<0.001), specifically for the choices of lisinopril vs hydrochlorothiazide, lisinopril vs amlodipine, candesartan vs hydrochlorothiazide, and candesartan vs amlodipine. On average, personalized treatment had the potential to provide an additional 4.4 mm Hg–lower systolic blood pressure. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
HCTZ 25 mg Half doses given weeks 1 and 2 of each treatment period, and full doses weeks 3 through 9	Patients were pharmacologically untreated or used BP-lowering monotherapy at the inclusion visit			
Van Bortel et al.[131] (2008) ACE inhibitor, ARB, β-blocker, calcium channel blocker, or placebo vs nebivolol	MA 12 RCTs involving >25 patients with essential HTN where nebivolol 5 mg QD was compared to placebo or other active drugs for >1 month	N=2,653 Duration varied	Primary: Antihypertensive effect and tolerability Secondary: Not reported	Primary: Overall, higher response rates were observed with nebivolol than all other antihypertensive agents combined (OR, 1.41; 95% CI, 1.15 to 1.73; P=0.001) and compared to the ACE inhibitors (OR, 1.92; 1.30 to 2.85; P=0.001), but response rates to nebivolol were similar to β-blockers (OR, 1.29; 95% CI, 0.81 to 2.04; P=0.283), calcium channel blockers (OR, 1.19; 95% CI, 0.83 to 1.70; P=0.350) and losartan (OR, 1.35; 95% CI, 0.84 to 2.15; P=0.212). Overall, a higher percentage of patients obtained normalized blood pressure with nebivolol compared to the other antihypertensive agents combined (OR, 1.35; 95% CI, 1.07 to 1.72; P=0.012). A higher percentage of patient receiving nebivolol obtained normalized blood pressure compared to losartan (OR, 1.98; 95% CI, 1.24 to 3.15; P=0.004) and calcium channel blockers (OR, 1.96; 95% CI, 1.05 to 1.96; P=0.024), but not when compared to other β-blockers (OR, 1.29; 95% CI, 0.81 to 1.65; P=0.473). Overall, the percentage of adverse events was significantly lower with nebivolol compared to the other antihypertensive agents combined (OR, 0.59; 95% CI, 0.48 to 0.72; P<0.001) and similar to placebo (OR, 1.16; 95% CI, 0.76 to 1.67; P=0.482). In comparing nebivolol to the individual treatments, nebivolol had a lower percentage of adverse events compared to losartan (OR, 0.52; 95% CI, 0.30 to 0.89; P=0.016), the other β-blockers (OR, 0.56; 95% CI, 0.36 to 0.85; P=0.007) and calcium channel blockers (OR, 0.49; 95% CI 0.33 to 0.72; P<0.001), but was similar to ACE inhibitors (OR, 0.75; 95% CI 0.52 to 1.08).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Baguet et al.[132] (2007) Antihypertensive drugs (enalapril, ramipril, trandolapril, candesartan, irbesartan, losartan, olmesartan, telmisartan, valsartan, HCTZ, indapamide SR*, atenolol, amlodipine, lercanidipine*, manidipine*, enalapril, ramipril, trandolapril, and aliskiren) Drugs were used as monotherapy, either at a fixed daily dosage or in increasing dosages. Although cicletanine*, furosemide and spironolactone were considered for inclusion, none	MA Patients greater than 18 years of age with mild or moderate essential HTN (SBP 140 to 179 mm Hg and/or DBP 90 to 109 mm Hg)	N=10,818 8 to 12 weeks	Primary: Weighted average reductions in SBP and DBP Secondary: Not reported	Primary: Data did not reflect outcomes from direct, head-to-head comparative trials or formal comparisons between drugs. Diuretics (-19.2 mm Hg; 95% CI, -20.3 to -18.0), calcium channel blockers (-16.4 mm Hg; 95% CI, -17.0 to -15.8) and ACE inhibitors (-15.6 mm Hg; 95% CI, -17.6 to -13.6) produced the greatest reductions in SBP from baseline (P values not reported). The magnitude of DBP reductions were generally similar among all drug classes; however, the greatest reductions in DBP from baseline were observed with the β-blocker, atenolol (-11.4 mm Hg; 95% CI, -12.0 to -10.9), calcium channel blockers (-11.4 mm Hg; 95% CI, -11.8 to -11.1) and diuretics (-11.1 mm Hg; 95% CI, -11.7 to -10.5) (P values were not reported). The weighted average reduction of SBP and DBP for each drug class were as follows: Diuretics: -19.2 (95% CI, -20.3 to -18.0) and -11.1 mm Hg (95% CI, -11.7 to -10.5), respectively. β-blockers: -14.8 (95% CI, -15.9 to -13.7) and -11.4 mm Hg (95% CI, -12.0 to -10.9), respectively. Calcium channel blockers: -16.4 (95% CI, -17.0 to -15.8) and -11.4 mm Hg (95% CI, -11.8 to -11.1), respectively. ACE inhibitors: -15.6 (95% CI, -17.6 to -13.6) and -10.8 mm Hg (95% CI, -11.9 to -9.7), respectively. ARBs: -13.2 (95% CI, -13.6 to -12.9) and -10.3 mm Hg (95% CI, -10.5 to -10.1), respectively. Renin inhibitor: -13.5 (95% CI, -14.2 to -12.9) and -11.3 mm Hg (95% CI, -11.7 to -10.9), respectively. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
of the trials relating to these agents satisfied all inclusion criteria.				
Diabetes/Diabetic Nephropathy/Renal Dysfunction				
Bakris et al.[133] (2010) ACCOMPLISH Benazepril and amlodipine 40-5 to 40-10 mg/day, followed by forced titration after 1 month on benazepril and amlodipine 20-5 mg (fixed-dose combination product) vs benazepril and HCTZ 40-12.5 to 40-25 mg/day, followed by forced titration after 1 month on benazepril and HCTZ 20-12.5 mg (fixed-dose combination product)	Prespecified subanalysis of ACCOMPISH Men and women >60 years of age with HTN and at high risk for cardiovascular events (history of coronary events, MI, revascularization, or stroke; impaired renal function; PAD, left ventricular hypertrophy; or diabetes)	N=11,482 2.9 years (mean duration)	Primary: Time to first event of doubling of serum creatinine concentration or end stage renal disease (defined as eGFR <15 mL/min/1.73 m^2 or need for chronic dialysis) Secondary: Progression of chronic kidney disease plus death, change in albuminuria, and change in eGFR	Primary: There were fewer chronic kidney disease events in the benazepril and amlodipine group (2.0% of patients) compared to the benazepril and HCTZ group (3.7%; HR, 0.52; 95% CI, 0.41 to 0.65; P<0.0001). Secondary: The composite endpoint of progression of chronic kidney disease and all-cause mortality was lower in the benazepril and amlodipine group (6.0%) compared to the benazepril and HCTZ group (8.1%; HR, 0.73; 95% CI, 0.64 to 0.84; P<0.0001). There was a slower decline in eGFR in the benazepril and amlodipine group compared to the benazepril and HCTZ group (-0.88 vs -4.22 mL/min/1.73 m^2; P=0.01). Of the patients with baseline microalbuminuria, there was a reduction in the urinary albumin:creatinine in the benazepril and HCTZ group of -63.8% (median change) compared to a median change of -29.0% in the benazepril and amlodipine group (P<0.0001). There was a higher percentage of patients reporting peripheral edema in the benazepril and amlodipine group compared to the benazepril and HCTZ group (P<0.0001).
Hou et al.[134] (2007) ROAD	OL, PRO, RCT Patients aged 18 to	N=360 3.7 years	Primary: Time to composite of doubling of	Primary: Compared to the conventional dosages, optimal antiproteinuric dosages of benazepril and losartan that were achieved through up-titration were

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Benazepril 10 mg/day vs individual up-titration (10 to 40 mg/day with median dose of 20 mg/day) or losartan 50 mg/day vs individual up-titration (50 to 200 mg/day with median dose of 100 mg/day) Up-titration was performed to optimal antiproteinuric and tolerated dosages, and then these dosages were maintained.	70 years with proteinuria and chronic renal insufficiency who did not have diabetes	(median follow-up)	serum creatinine, ESRD or death Secondary: Changes in level of proteinuria, rate of progression of renal disease	associated with a 51 and 53% reduction in the risk for the primary end point (P=0.028 and P=0.022, respectively). There was no statistically significant difference between benazepril and losartan in the overall relative risk reduction at their respective optimal antiproteinuric dosages or at conventional dosages. Secondary: Optimal antiproteinuric dosages of benazepril and losartan at comparable blood pressure control, achieved a greater reduction in both proteinuria and the rate of decline in renal function compared to their conventional dosages. There was no significant difference in proteinuria reduction between benazepril and losartan at both conventional and optimal antiproteinuric dosages. Changes in renal function were similar between benazepril and losartan arms at both conventional and optimal antiproteinuric doses (P>0.05). There was no significant difference for the overall incidence of major adverse events between groups that were given conventional and optimal dosages in any of the treatment arms.
Bakris et al.[135] (2008) GUARD Benazepril and HCTZ (fixed-dose combination) vs	DB, RCT Hypertensive, albuminuric type 2 diabetic patients, mean age 58 years were randomized to receive either initial fixed-dose combination product	N=322 52 weeks	Primary: Change in urinary albumin to creatinine ratio after 1 year of initial treatment with either fixed-dose combination, blood pressure reductions	Primary: Both combinations significantly reduced the urinary albumin to creatinine ratio compared to baseline (P<0.0001). The median percent change was -72.1% for benazepril and HCTZ and -40.5% for amlodipine and benazepril (P<0.0001). Both regimens significantly reduced SBP and DBP compared to baseline (P<0.0001). The mean reduction in both SBP and DBP was greater in the amlodipine-based arm than in the HCTZ-based arm; however, significance in favor of the amlodipine regimen was observed only for DBP (SBP,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
amlodipine and benazepril (fixed-dose combination)			Secondary: Proportion who progressed to overt diabetic nephropathy, safety	-20.5 vs -18.8; P=0.19; DPB, -13.1 vs -9.97; P=0.02). A greater proportion of patients who had microalbuminuria at baseline and treated with benazepril and HCTZ compared to amlodipine and benazepril attained normalization of the urinary albumin to creatinine ratio, defined as <30 mg/g (69.2 vs 47.8%; P=0.0004). Secondary: The percentage of patients progressing to overt proteinuria was similar for both groups. Overall, both study drugs were well tolerated. Adverse reactions possibly related to the study medications occurred in 11.4 and 3.6% of patients receiving amlodipine and benazepril and benazepril and HCTZ, respectively. They included peripheral edema (7.8 vs 2.4%, respectively), fatigue (1.2% in each group), pitting edema (1.2 vs 0.0%), face edema (0.6 vs 0.0%) and thirst (0.6 vs 0.0%). More patients receiving the HCTZ-based regimen (10.8%) discontinued study drug than with the amlodipine-based regimen due to side effects (5.4%).
Esnault et al.[136] (2008) Enalapril 5 to 20 mg/day vs amlodipine 5 to 10 mg QD	MC, DB, PC, RCT Nondiabetic, adult patients with estimated creatinine clearance of 20 to 60 ml/min	N=263 3 years	Primary: Change in GFR measured yearly by blood clearance Secondary: Composite of renal events and tolerability	Primary: No statistically significant difference was found between amlodipine and enalapril in GFR decline (-4.92 and -3.98 mL/min., respectively, at last observation). Secondary: No statistically significant difference was found between amlodipine and enalapril in the composite secondary end point after a median follow-up of 2.9 years, including in the subgroup of patients with proteinuria >1 g/d at baseline.
Barnett et al.[137] (2004) DETAIL Enalapril 20 mg/day vs	DB, MC, PG, RCT Patients aged 35 to 80 years with type 2 diabetes and HTN	N=250 5 years	Primary: Change in the GFR Secondary: Annual changes in GFR, serum creatinine level, urinary albumin	Primary: After five years, GFR decreased by 17.9 mL/minute/1.73 m^2 with telmisartan compared to 14.9 mL/min/1.73 m^2 with enalapril (mean difference, -3.0 mL/min/1.73 m^2; 95% CI, -7.6 to 1.6). Therefore, the changes in GFR were comparable between the groups. Secondary: The effects of the two agents on the secondary end points were not

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
telmisartan 80 mg/day			excretion, and blood pressure; rates of ESRD and cardiovascular events; all-cause mortality	significantly different after five years.
Mogensen et al.[138] (2000) CALM Lisinopril 20 mg QD vs candesartan 16 mg QD vs lisinopril 20 mg QD plus candesartan 16 mg QD Patients received 12 weeks monotherapy followed by an additional 12 weeks of monotherapy or combination therapy.	DB, DD, MC, PG, RCT Patients 30 to 75 years old with HTN, type 2 diabetes, and microalbuminuria	N=199 24 weeks	Primary: Blood pressure and urinary albumin:creatinine ratio Secondary: Not reported	Primary: At 12 weeks, mean reductions in DBP were 9.7 mm Hg (P<0.001) and 9.5 mm Hg (P<0.001), respectively, and in urinary albumin:creatinine ratio were 46% (P<0.001) and 30% (P<0.001) for lisinopril and candesartan, respectively. Compared to either agent alone, at 24 weeks the combination of lisinopril plus candesartan resulted in 16.3 mm Hg reduction in mean DBP vs 10.4 mm Hg for candesartan alone (P<0.001) and 10.7 mm Hg for lisinopril alone (P<0.001). The reduction in urinary albumin:creatinine ratio with combination treatment (50%) was greater than with lisinopril alone (39%; P<0.001) and candesartan alone (24%; P=0.05). All treatments were generally well tolerated. Secondary: Not reported
Fried et al.[139] (2013) VA NEPHRON-D	DB, MA, RCT Veterans with	N=1448 Median	Primary: First occurrence of a decline in the	The trial was stopped early because the absolute risk of serious adverse events appeared to be greater than the potential benefit of reducing primary end-point events.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Losartan with lisinopril vs losartan alone	proteinuric diabetic kidney disease, an estimated GFR of 30.0 to 89.9 ml/minute/1.73 m^2 , and a urinary albumin-to-creatinine ratio of ≥300	follow-up 2.2 years	eGFR (an absolute decrease of ≥30 ml/minute/1.73 m^2 if the eGFR was ≥60 ml/minute/1.73 m^2 at randomization or a relative decrease of ≥50% if the eGFR was <60 ml/minute/1.73 m^2), ESRD, or death Secondary: First occurrence of a decline in the eGFR or ESRD Tertiary: CV events, slope of change in eGFR, and change in albuminuria at 1 year	Primary: There were 152 primary end-point events in the monotherapy group (21.0%) and 132 in the combination-therapy group (18.2%).The risk of the primary end point did not differ significantly between the two groups. Secondary: There were 101 secondary end-point events (a decline in the estimated GFR or ESRD) in the monotherapy group (14.0%) and 77 events in the combination-therapy group (10.6%).There was no significant between-group difference in mortality or ESRD (Table 2), though the number of ESRD events was small. Tertiary: There was no significant difference in the rate of cardiovascular events between the two groups. There was no significant difference in treatment effect on the decline in the estimated GFR (P=0.17). During adjustment of the losartan dose, the median urinary albumin-to-creatinine ratio declined from 959 to 807 (P=0.001). There was a further decline from randomization to 1 year, with a greater decline in the combination-therapy group (from 786 to 517) than in the monotherapy group (from 829 to 701) (P<0.001).
DREAM Trial Investigators[140] (2006) DREAM Ramipril up to 15 mg/day vs placebo	DB, MC, PC, PRO, RCT, 2-by-2 factorial design Adults aged 30 years or more with impaired fasting glucose and/or impaired glucose tolerance and no previous cardiovascular	N=5,269 3 years (median)	Primary: Composite of newly diagnosed diabetes or death Secondary: Regression to normoglycemia, glucose levels, composite of cardiac and renal events (were not	Primary: The composite primary outcome did not differ significantly between the ramipril group (18.1%; HR, 0.91; 95% CI, 0.81 to 13; P=0.15) and the placebo group (19.5%). Secondary: Participants receiving ramipril were more likely to have regression to normoglycemia than those receiving placebo (HR, 1.16; 95% CI, 17 to 1.27; P=0.001). At the end of the study, the median fasting plasma glucose level was not significantly lower in the ramipril group than in the placebo group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	disease		yet analyzed at the time of this publication)	(P=0.07), though plasma glucose levels two hours after an oral glucose load were significantly lower in the ramipril group (P=0.01).
GISEN Group[141] (1997) REIN Ramipril 1.25 mg/day vs placebo	DB, PC, RCT Patients between 18 and 70 years who were either normotensive (<140/90 mm Hg) or hypertensive with chronic nephropathy and persistent proteinuria, who had not received ACE inhibition therapy for ≥2 months	N=166 16 months	Primary: Rate of GFR decline, extent to which this effect was dependent on the drug's antiproteinuric effect Secondary: Blood pressure control, time to doubling of baseline serum creatinine or progression to end-stage renal failure, cardiovascular complications, total and cardiovascular mortality	Primary: Mean rate of GFR decline per month was significantly lower in the ramipril group than in the placebo group (0.53 mL/min vs 0.88 mL/min; P=0.03). Among the ramipril-assigned patients, percentage reduction in proteinuria was inversely correlated with decline in GFR (P=0.035) and predicted the reduction in risk of doubling of baseline creatinine or end-stage renal failure (18 ramipril vs 40 placebo; P=0.04). Secondary: Blood pressure control and the overall number of cardiovascular events were similar in the two treatment groups. Fifty-eight patients (18 in the ramipril group and 40 in the placebo group) reached the combined end point of doubling of baseline serum creatinine concentration or end-stage renal failure (P=0.02). The risk of progression was still significantly reduced after adjustment for changes in SBP (P=0.04) and DBP (P=0.04) with ramipril, but not after adjustment for changes in proteinuria. Note: Originally, 352 patients were placed into stratum 1 (urinary protein excretion exceeding 1 g/24 hours) or stratum 2 (urinary protein excretion exceeding 3.0 g/24 hours). At the second planned interim analysis, the difference in decline in GFR between the ramipril and placebo groups in stratum 2 was highly significant (P=0.001). The Independent Adjudicating Panel therefore decided to open the randomization code and do the final analysis in this stratum while stratum 1 continued in the trial.
Uresin et al.[142] (2007) Aliskiren 150 to 300 mg QD	DB, MC, RCT Patients ≥18 years of age with type 1 or type 2 diabetes mellitus and stage 1	N=837 8 weeks	Primary: Change in mean sitting DBP Secondary: Change in mean	Primary: Aliskiren monotherapy, ramipril monotherapy, and aliskiren and ramipril combination therapy lowered mean sitting DBP by 11.3, 10.7, and 12.8 mm Hg, respectively. Treatment with aliskiren and ramipril combination therapy produced significantly greater reductions from baseline in mean sitting DBP compared to either aliskiren monotherapy (P=0.043) or

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ramipril 5 to 10 mg QD vs aliskiren 150 to 300 mg and ramipril 5 to 10 mg QD	to 2 HTN (mean sitting DBP) >95 and <110 mm Hg)		sitting SBP, proportion of patients with a successful response to treatment (trough mean sitting DBP <90 mm Hg and/or ≥10 mm Hg reduction from baseline), rates of blood pressure control (blood pressure <130/80 mm Hg), changes from baseline in 24-hour ABPM measurements, and changes in biomarkers (plasma renin concentration, plasma renin activity, aldosterone)	ramipril monotherapy (P=0.004). Aliskiren 300 mg was statistically non-inferior (P=0.0002) to ramipril 10 mg for the change in mean sitting DBP. Secondary: Aliskiren monotherapy, ramipril monotherapy, and aliskiren and ramipril combination therapy lowered mean sitting SBP by 14.7, 12.0, and 16.6 mm Hg, respectively. Treatment with aliskiren and ramipril combination therapy produced significantly greater reductions from baseline in mean sitting SBP compared to ramipril monotherapy (P<0.0001), but not aliskiren monotherapy (P=0.088). Aliskiren monotherapy was statistically superior to ramipril for the change in mean sitting SBP (P=0.021). The proportion of patients with a successful response to therapy was similar for aliskiren and ramipril combination therapy (74.1%) and aliskiren monotherapy (73.1%). The responder rates in both groups were significantly higher (P<0.05) compared to ramipril monotherapy (65.8%). Rates of blood pressure control with aliskiren and ramipril combination pressure (13.1%) were not significantly different compared to aliskiren monotherapy (8.2%) or ramipril monotherapy (8.4%). All treatments significantly lowered mean 24-hour ambulatory blood pressure. Aliskiren and ramipril combination therapy was significantly more effective compared to ramipril monotherapy in lowering 24-hour mean ambulatory DBP (P=0.034). There was no significant difference in 24-hour ambulatory SBP compared to ramipril monotherapy. Aliskiren significantly reduced plasma renin activity from baseline as monotherapy (by 66%, P<0.0001) or in combination with ramipril (by 48%, P<0.0001).
Agodoa et al.[143] (2001) AASK Ramipril 2.5 to 10 mg QD	DB, MC, RCT African American patients, age 18 to 70 years old, with hypertensive renal disease (GFR 20 to	N=1,094 4 years	Primary: Rate of change in GFR (GFR slope) Secondary: Composite of: confirmed	Primary: The average decline in GFR was slower, by 36% in the ramipril group as compared to the amlodipine group (P=0.002). However, during the first three months, GFR increased more in the amlodipine group than the ramipril group (P<0.001). The mean total slope did not differ between the groups (P=0.38).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs amlodipine 5 to 10 mg QD	65 mL/min)		reduction GFR by 50% or by 25 mL/min for baseline, ESRD	Secondary: The risk reduction for the composite secondary outcome was significantly greater for the ramipril group than the amlodipine group (P=0.005). The rate of ESRD was significantly lower in the ramipril group (P=0.01).
Wright et al.[144] (2002) AASK Ramipril 2.5 to 10 mg/day vs amlodipine 5 to 10 mg/day vs metoprolol 50 to 200 mg/day	DB, MC, RCT Patients were self-identified African Americans aged 18 to 70 years with HTN and a GFR between 20 and 65 mL/min/ 1.73 m^2 and no other identified cause of renal insufficiency	N=1,094 3-6.4 years	Primary: Rate of change in GFR (grouped by usual blood pressure [MAP goal 102 to 107 mm Hg] vs lower blood pressure [≤92 mm Hg]) Secondary: Clinical composite outcome (reduction in GFR by 50% or more, ESRD, or death)	Primary: No significant difference in primary outcome was reported between the usual blood pressure group compared to the lower blood pressure group (P=0.24). None of the drug group comparisons showed consistently significant differences in the GFR slope. Secondary: The lower blood pressure goal did not significantly reduce the rate of the clinical composite outcome (risk reduction for lower blood pressure group, 2%; 95% CI, -22 to 21; P=0.85). Ramipril resulted in significant risk reductions in the clinical composite outcomes compared to amlodipine (38%; 95% CI, 14 to 56; P=0.004) and metoprolol (22%; 95% CI, 1 to 38; P=0.04). There was no significant difference in the clinical composite outcome between the amlodipine and metoprolol groups.
Bianchi et al.[145] (2010) Ramipril 10 mg and atorvastatin 10 mg QD (conventional therapy) vs spironolactone 25 mg, ramipril 10 mg, irbesartan 300	RCT, OL Patients with a clinical diagnosis of idiopathic chronic glomerulonephritis and urine protein-creatinine ratio >1 g/g	N=128 36 months	Primary: Changes over time in proteinuria and eGFR Secondary: Adverse events, drop outs	Primary: SBP decreased more in the intensive-therapy group (from 156.6 to 113.5 mm Hg) than in the conventional therapy group (from 155.7 to 122.7 mm Hg; P<0.01). Urine protein excretion decreased from 2.65 to 0.45 g/g creatinine with intensive therapy (P<0.001). With conventional therapy, urine protein excretion decreased from 2.60 to 1.23 g/g creatinine (P<0.001). With intensive therapy, eGFR did not significantly change over time (64.6 vs 62.9 mL/min/1.73 m^2). With conventional therapy, eGFR decreased from 62.5 to 55.8 mL/min/1.73 m^2 (P<0.01). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg, and atorvastatin 10 mg QD (intensive therapy) The addition of diuretics, calcium antagonists, β-blockers or α1-receptor antagonists were added to achieve blood pressure <130/80 mm Hg				In the conventional therapy group, eight patients discontinued the study due to hyperkalemia, cough, and rapid deterioration in kidney function. In the intensive therapy group, 15 dropped out due to hyperkalemia, cough, and hypotension. Nine patients in the intensive therapy group developed gynecomastia. Twelve patients on conventional and 31 on intensive therapy had to interrupt the study temporarily because of low blood pressure. No patient developed an increase in creatine kinase, alanine aminotransferase, and alkaline phosphatase levels during the study.
Chrysostomou et al.[146] (2006) Ramipril 5 mg/day plus spironolactone 25 mg/day and placebo vs ramipril 5 mg/day plus irbesartan 150 mg/day and placebo vs ramipril 5 mg/day plus placebo and placebo	DB, PC, RCT Patients 18 to 75 years of age, with a 24 hour urinary protein excretion >1.5 g/24 hours on ≥2 occasions ≥3 months apart, serum creatinine level ≤200 µmol/L with <20% variability in the preceding 3 months and treatment with an ACE inhibitor ≥6 months	N=41 6 months	Primary: Change in 24 hour urinary protein excretion at three months Secondary: Change in 24 hour urinary protein excretion at six months, change in blood pressure and creatinine clearance, adverse effects	Primary: Compared to ramipril-treated patients, the 24 hour urinary protein excretion reduction at three months was significantly greater in ramipril plus spironolactone-treated patients (P=0.004). Ramipril-, irbesartan- and spironolactone-treated patients exhibited a significant reduction in 24 hour urinary protein excretion compared to ramipril-treated patients (P<0.001). There was no significant difference in 24 hour urinary protein excretion with ramipril- and ramipril plus irbesartan-treated patients (P=1.00). At three months, spironolactone-treated patients exhibited a significant reduction in proteinuria from baseline (P≤0.001). In contrast, non-spironolactone-treated patients did not experience a significant reduction in proteinuria from baseline (P=0.840). Secondary: At six months, spironolactone-treated patients exhibited the greatest reduction in proteinuria compared to the other treatments (P<0.05). At six months, DBP was higher among ramipril monotherapy-treated patients compared to the other treatments (P=0.046). There was no

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs spironolactone 25 mg/day plus irbesartan 150 mg/day and ramipril 5 mg/day				difference in SBP among the treatments (P value not reported). There were no differences in creatinine clearance among the treatments (P>0.05). Gynecomastia was not observed with any of the treatments.
Nakao et al.[147] (2003) COOPERATE Trandolapril 3 mg/day vs losartan 100 mg/day vs trandolapril and losartan at equivalent doses	DB, MC, PC, RCT Patients aged 18 to 70 years with chronic nephropathy (nondiabetic renal disease)	N=263 3 years	Primary: Composite of time to doubling of serum creatinine or ESRD Secondary: Changes in blood pressure, daily urinary protein excretion, adverse effects	Primary: The combined end point was reached in 11% of patients in the combination trandolapril and losartan group compared to 23% of patients in the trandolapril (P=0.018) and 23% of patients in the losartan group (P=0.016). Secondary: Mean SBP and DBP reductions were similar among the three treatment groups (P=0.109). All patients receiving active treatment had significant decreases in urinary protein excretion, but the greatest difference was seen with the combination trandolapril and losartan group compared to trandolapril or losartan (-75.6, -44.3, and -42.1%, respectively; P=0.01). The frequency of adverse events did not differ between groups, although a slightly higher occurrence of hyperkalemia and dry cough was recorded in the trandolapril and combination groups than in the losartan group.
Ruggenenti et al.[148] (2004) BENEDICT Trandolapril 2 mg/day vs verapamil SR 240 mg/day	DB, MC, RCT Patients ≥40 years with type 2 diabetes (not exceeding 25 years) and HTN (SBP ≥130 mm Hg and/or DBP ≥85 mm Hg) but with normoalbuminuria (urinary albumin excretion rate of <20	N=1,204 3.6 years (median)	Primary: Development of persistent microalbuminuria comparing combination therapy to placebo, acceleration factor Secondary: Primary end point comparing	Primary: The primary outcome was reached in 5.7% of patients receiving combination therapy vs 10.0% for patients receiving placebo. The estimated acceleration factor (which quantifies the effect of one treatment relative to another in accelerating or slowing disease progression) adjusted for predefined baseline characteristics was 0.39 for the comparison between verapamil plus trandolapril and placebo (P=0.01). Secondary: The primary outcome was reached in 6.0% of patients receiving trandolapril, 11.9% receiving verapamil, and 10.0% receiving placebo. The estimated acceleration factor was 0.47 for trandolapril vs placebo

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs trandolapril and verapamil SR 2-180 mg/day (fixed-dose combination) vs placebo	mcg/minute)		trandolapril and verapamil monotherapy to placebo, blood pressure, adverse events	(P=0.01) and 0.83 for verapamil vs placebo (P=0.54). Trandolapril plus verapamil and trandolapril alone delayed the onset of microalbuminuria by factors of 2.6 and 2.1, respectively. Throughout the study the average trough SBP/DBP was 139/80 mm Hg for patients receiving trandolapril plus verapamil, 139/81 mm Hg for trandolapril, 141/82 mm Hg for verapamil and 142/83 mm Hg for placebo. The comparison was significant (P≤0.002) between trandolapril plus verapamil or trandolapril alone vs placebo, but not for verapamil vs placebo. Serious adverse events were similar in all treatment groups.
Casas et al.[149] (2005) ACE inhibitor or ARBs compared to placebo vs ACE inhibitor or ARBs compared to other antihypertensive drugs (β-adrenergic blocking agents, α-adrenergic blocking agents, calcium-channel blocking agents, or combinations) Specific agents and doses were	MA (127 trials) Studies in adults that examined the effect of any drug treatment with a blood pressure lowering action on progression of renal disease	N=not reported 4.2 years (mean)	Primary: Doubling of serum creatinine, and ESRD Secondary: Serum creatinine, urine albumin excretion and GFR	Primary: Treatment with ACE inhibitors or ARBs resulted in a nonsignificant reduction in the risk of doubling of creatinine vs other antihypertensives (P=0.07) with no differences in the degree of change of SBP or DBP between the groups. A small reduction in ESRD was observed in patients receiving ACE inhibitors or ARBs compared to other antihypertensives (P=0.04) with no differences in the degree of change of SBP or DBP between the groups. Secondary: Small reductions in serum creatinine and in SBP were noted when ACE inhibitors or ARBs were compared to other antihypertensives (P=0.01). Small reduction in daily urinary albumin excretion in favor of ACE inhibitor or ARBs were reported when these agents were compared to other antihypertensives (P=0.001). Compared to other drugs, ACE inhibitors or ARBs had no effect on the GFR.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
not specified.				
Strippoli et al.[150] (2004) ACE inhibitors vs placebo or ARBs vs placebo or ACE inhibitors vs ARBs	MA Patients with diabetic nephropathy	43 trials ≥6 months (range 6 to 63.6 months)	Primary: All-cause mortality, renal outcomes (ESRD, doubling of serum creatinine, microalbuminuria to macroalbuminuria) Secondary: Not reported	Primary: ACE inhibitors significantly reduced all-cause mortality compared to placebo or no treatment (RR, 0.79; 95% CI, 0.63 to 0.99; P=0.04). There was a nonsignificant trend for reduction in ESRD (P=0.07) and doubling of serum creatinine (P=0.08) with ACE inhibitors compared to placebo or no treatment. ACE inhibitors significantly reduced the risk of progression from microalbuminuria to macroalbuminuria (P=0.0007) and increased regression back to normoalbuminuria (P<0.0001) compared to placebo or no treatment. ARBs did not significantly reduce all-cause mortality compared to placebo or no treatment (RR, 0.99; 95% CI, 0.85 to 1.17; P=0.95). ARBs significantly reduced the risk of ESRD (P=0.001) and doubling of serum creatinine (P=0.004). ARBs significantly decreased the risk of progression to macroalbuminuria (P=0.001) and increased regression to normoalbuminuria (P=0.02) compared to placebo or no treatment. The three trials that compared ACE inhibitors to ARBs did not report on all-cause mortality, ESRD or doubling of serum creatinine. Progression from microalbuminuria to macroalbuminuria was reported in one trial (N=92) and there was no significant difference in risk, with the point estimate favoring ACE inhibitors (RR, 0.16; 95% CI, 0.02 to 1.44). Regression from microalbuminuria to normoalbuminuria in 1 trial showed a nonsignificant difference in the risk. Secondary: Not reported
Strippoli et al.[151] (2006) ACE inhibitors vs placebo	MA Patients with diabetic kidney disease	N=12,067 (49 trials) ≥6 months	Primary: All-cause mortality, ESRD, doubling of serum creatinine concentration, progression from micro- to macroalbuminuria,	Primary: There was no significant difference in the risk of all-cause mortality for ACE inhibitors vs placebo or no treatment (RR, 0.91; 95% CI, 0.71 to 1.17) and ARBs vs placebo or no treatment (RR, 0.99; 95% CI, 0.85 to 1.17). No statistically significant reduction in the risk of all-cause mortality was found in the three studies that compared ACE inhibitors with ARBs (RR, 0.92; 95% CI, 0.31 to 2.78). A subgroup analysis of studies showed a significant reduction in the risk

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
or ARBs vs placebo or ACE inhibitors vs ARBs			regression from micro- to normoalbuminuria, drug-related toxicity (including cough, headache, hyperkalemia, impotence and pedal edema) Secondary: Not reported	of all-cause mortality with the use of full-dose ACE inhibitors (RR, 0.78; 95% CI, 0.61 to 0.98) but not when using half or less than half the maximum tolerable dose of ACE inhibitors (RR, 1.18; 95% CI, 0.41 to 3.44). There was a significant reduction in the risk of ESRD with ACE inhibitors and ARBS compared to placebo or no treatment (RR, 0.60; 95% CI, 0.39 to 0.93 and RR, 0.78; 95% CI, 0.67 to 0.91, respectively). There was a significant reduction in the risk of doubling of serum creatinine concentration with ACE inhibitors and ARBS (RR, 0.68; 95% CI, 0.47 to 10 and RR, 0.79; 95% CI, 0.67 to 0.93, respectively). ACE inhibitors and ARBS significantly reduced the risk of progression from micro- to macroalbuminuria (RR, 0.45; 95% CI, 0.29 to 0.69 and RR, 0.49; 95% CI, 0.32 to 0.75, respectively). ACE inhibitors and ARBS significantly increased the regression from micro- to normoalbuminuria compared to placebo or no treatment (RR, 3.06; 95% CI, 1.76 to 5.35 and RR, 1.42; 95% CI, 15 to 1.93, respectively). The seven studies that compared ACE inhibitors to ARBS did not report the outcome of ESRD or doubling of serum creatinine. Progression from micro- to macroalbuminuria and from micro- to normoalbuminuria were evaluated each in one trial and showed a nonsignificant difference in the risk between ACE inhibitors and ARBS. ACE inhibitors were associated with a significant increase in the risk of cough but not hyperkalemia, headache or impotence when compared to placebo or no treatment. ARBS were associated with a significant increase in the risk of hyperkalemia but not cough or headache compared to placebo or no treatment. Secondary: Not reported
Miscellaneous				
Montalescot et al.[152] (2009)	AC, DB, MC, RCT Adults with non-ST	N=429 60 days	Primary: Change from baseline in high-	Primary: High-sensitivity C-reactive protein levels were comparable in both treatment groups (irbesartan: 15.2 mg/L at baseline, 6.5 mg/L at day 60;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ARCHIPELAGO Enalapril 10 mg QD, followed by 20 mg QD on day 15 vs irbesartan 150 mg QD, followed by 300 mg QD on day 15	elevation ACS		sensitivity C-reactive protein at day 60 Secondary: Changes in other inflammatory markers such as troponin I	absolute change of -8.7 mg/L; enalapril: 12.6 mg/L at baseline, 5.5 mg/L at day 60; absolute change of -7.1 mg/L, P value not significant). Secondary: Similarly, mean levels of markers of myocardial injury (troponin I) and endothelial dysfunction (microalbuminuria) also decreased from baseline to day 60, with no significant differences between treatment groups.
Dagenais et al.[153] (2008) Ramipril 15 mg or rosiglitazone 8 mg QD vs placebo	DB, PC, RCT Adults >30 years with impaired fasting glucose or impaired glucose tolerance without known cardiovascular disease or renal insufficiency	N=5,269 3 years	Primary: Composite cardiorenal outcome (first occurrence of any cardiovascular death, nonfatal MI, stroke, new heart failure, progression to microalbuminuria or proteinuria, renal insufficiency requiring dialysis or transplantation) Secondary: Subcomponents of the primary analysis	Primary: Compared to placebo, neither ramipril (15.7 vs 16.0%; HR, 0.98; P=0.75) nor rosiglitazone (15.0 vs 16.8%; HR, 0.87; P=0.07) reduced the risk of the cardiorenal composite outcome. Secondary: Ramipril had no impact on the cardiovascular disease and renal components. Rosiglitazone increased heart failure (0.53 vs 0.08%; HR, 7.04; P=0.01), but reduced the risk of the renal component (HR, 0.80; P=0.005).
Belluzzi et al.[154] (2009) Ramipril 5mg QD	DB, PC, RCT Adults with lone atrial fibrillation	N=62 3 years	Primary: Relapse of atrial fibrillation as determined by	Primary: At the end of the study, atrial fibrillation relapses were observed in three ramipril-treated patients and in 10 control patients (P<0.03).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	without heart disease or HTN		clinical assessment, ECG, 24 hour Holter monitor, and questionnaire collection. Secondary: Not reported	Secondary: Not reported
Hansson et al.[155] (1998) HOT Aspirin 75 mg QD vs placebo A 5 step antihypertensive treatment regimen: 1) felodipine 5 mg QD, 2) ACE inhibitor or β-blocker, 3) dose titrations, 4) dose titrations, 5) diuretic.	MC, RCT, OL Adults with HTN and a DBP between 100 and 115 mm Hg	N=18,790 3.8 years	Primary: Major cardiovascular events (fatal and nonfatal, fatal and nonfatal stroke, and all other cardiovascular deaths) Secondary: Not reported	Primary: There were 9.9, 10.0, and 9.3 major cardiovascular events per 1,000-patients years, respectively, in the DBP ≤90, DBP ≤85, and DBP ≤80 treatment groups (P=0.50), thus suggesting that the reduction of DBP below 90 mm Hg does not provide any mortality or morbidity advantage. Aspirin reduced major cardiovascular events by 15% (P=0.03) and all MI by 36% (P=0.002), with no effect on stroke. There were seven fatal bleeds in the aspirin group and eight in the placebo group, and 129 versus 70 non-fatal major bleeds in the two groups, respectively (P<0.001). Secondary: Not reported

*Agent not available in the United States.
Drug regimen abbreviations: BID=twice daily, ER=extended-release, QD=once daily, SR=sustained-release, TID=three times daily
Study design abbreviations: AC=active-controlled, BE=blinded endpoint, DB=double blind, DD=double dummy, MA=meta-analysis, MC=multicenter, OL=open label, OS=observational, PC=placebo controlled, PG=parallel group, PRO=prospective, RETRO=retrospective, RCT=randomized controlled trial, SB=single-blind, XO=crossover
Miscellaneous abbreviations: ABPM=ambulatory blood pressure monitoring, ACE inhibitor=angiotensin converting enzyme inhibitor, ACS=acute coronary syndrome, ARB=angiotensin II receptor blocker, BMI=body mass index, CAD=coronary artery disease, CHD=coronary heart disease, CHF=congestive heart failure, CI=confidence interval, DBP=diastolic blood pressure, ECG=electrocardiogram, eGFR=estimated glomerular filtration rate, ESRD=end stage renal disease, GFR=glomerular filtration rate, HCTZ=hydrochlorothiazide, HDL-C=high-density lipoprotein cholesterol, HR=hazard ratio, HTN=hypertension, IV=intravenous, LDL-C=low-density lipoprotein cholesterol, LVEF=left ventricular ejection fraction, MAP=mean arterial pressure, MI=myocardial infarction, MMSE=Mini Mental State Examination, MRI=magnetic resonance imaging, NIDDM=non-insulin dependent diabetes mellitus, NNT=number needed to treat, NYHA=New York Heart

Association, OR=odds ratio, PAD=peripheral arterial disease, PCI=percutaneous coronary intervention, PVD=peripheral vascular disease, QOL=quality of life, RR=relative risk, SBP=systolic blood pressure, TC=total cholesterol, TG=triglyceride, TIA=transient ischemic attack, WHO=World Health Organization

Additional Evidence

Dose Simplification
Taylor et al. evaluated adherence rates with amlodipine and benazepril fixed-dose combination compared to an ACE inhibitor plus a long-acting dihydropyridine administered as separate formulations. There was no significant difference in adherence in younger subjects (18 to 39 year olds); however, in all age group combined, adherence rates were higher with amlodipine and benazepril compared to the use of an ACE inhibitor plus a long-acting dihydropyridine (80.8 vs 73.8%; P<0.001).[156] Dickson et al. evaluated adherence rates with amlodipine and benazepril fixed-dose combination compared to an ACE inhibitor plus a long-acting dihydropyridine administered as separate formulations in an elderly Medicaid population. Over a 12 month period, adherence rates were reported to be significantly higher with fixed-dose combination product compared to the administration of an ACE inhibitor and dihydropyridine as separate formulations (63.4 vs 49.0%; P<0.0001).[157] Dezzi et al. also reported significantly higher compliance rates at 12 months in patients receiving fixed-dose lisinopril and hydrochlorothiazide (68.7%) or enalapril and hydrochlorothiazide (70.0%) vs administration of the components as separate formulations (57.8 and 57.5%, respectively; P<0.05 for both comparisons).[158]

Stable Therapy
Sapienza et al. evaluated the impact of converting long-term care patients from high-dose calcium-channel blockers or ACE inhibitor plus calcium-channel blockers to a fixed-dose combination of amlodipine/benazepril. There was no significant change in blood pressure from baseline following the conversion; however, there was a significant reduction (81.8%) in the number of patients reporting ≥1 drug-related adverse event (22 vs 4; P<0.05), particularly edema (75% reduction).[159]

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 12. Relative Cost of the Angiotensin-Converting Enzyme Inhibitors

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Benazepril	tablet	Lotensin®*	$$$	$
Captopril	tablet	N/A	N/A	$$$
Enalapril	solution, tablet	Epaned®*, Vasotec®*	$$$$$	$$$
Fosinopril	tablet	N/A	N/A	$
Lisinopril	solution, tablet	Prinivil®*, Qbrelis®, Zestril®*	$$$$$	$
Moexipril	tablet	N/A	N/A	$$$$
Perindopril	tablet	N/A	N/A	$
Quinapril	tablet	Accupril®*	$$$$	$
Ramipril	capsule	Altace®*	$$$$$	$
Trandolapril	tablet	N/A	N/A	$$
Combination Products				
Benazepril and HCTZ	tablet	Lotensin HCT®*	$$$	$
Captopril and HCTZ	tablet	N/A	N/A	$$$$
Enalapril and HCTZ	tablet	Vaseretic®*	$$$$$	$
Fosinopril and HCTZ	tablet	N/A	N/A	$$$
Lisinopril and HCTZ	tablet	Prinzide®*, Zestoretic®*	$$$$	$
Quinapril and HCTZ	tablet	Accuretic®*	$$$$	$$

*Generic is available in at least one dosage form or strength.
HCTZ=hydrochlorothiazide, N/A=not available

X. Conclusions

All of the angiotensin-converting enzyme (ACE) inhibitors are approved for the treatment of hypertension. Some of the products are also approved for the treatment of diabetic nephropathy, heart failure, and post-myocardial infarction.[3-18] The ACE inhibitors are available as single entity products, as well as in combination with hydrochlorothiazide. All of the products are available in a generic formulation.

There are numerous national and international guidelines that recommend the use of ACE inhibitors in patients with the following conditions: acute coronary syndrome, cerebrovascular disease, coronary artery disease, diabetes, diabetic nephropathy, heart failure, hypertension, left ventricular dysfunction, left ventricular hypertrophy, previous myocardial infarction, and renal disease. In general, guidelines do not give preference to one ACE inhibitor over another.[19-37] Thiazide-type diuretics are frequently recommended as initial therapy in patients with uncomplicated hypertension.[29-34] According to the National Heart, Lung, and Blood Institute's Eighth Report of The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8), thiazide-type diuretics should be utilized first-line for most patients with hypertension, either alone or in combination with another hypertensive from a different medication class (e.g., ACE inhibitors, ARBs, β-blockers, calcium channel blockers).[29] Several guidelines consistently recommend that the selection of an antihypertensive agent be based on compelling indications for use.[29-37] Most patients will require more than one antihypertensive medication to achieve blood pressure goals.[29-36]

In clinical trials, the ACE inhibitors have been shown to reduce cardiovascular morbidity and mortality, preserve renal function in patients with nephropathy, and effectively lower blood pressure when administered as monotherapy or in combination with other antihypertensive agents.[38-150] Most patients will need more than one antihypertensive agent to achieve blood pressure goals. The use of a fixed-dose combination product may simplify the treatment regimen and improve adherence.[29-34,156-158] However, there are no prospective, randomized trials that have demonstrated better clinical outcomes with a fixed-dose combination product compared to the coadministration of the individual components as separate formulations.

There is insufficient evidence to support that one brand angiotensin-converting enzyme inhibitor is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand angiotensin-converting enzyme inhibitors within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand angiotensin-converting enzyme inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Angiotensin II Receptor Antagonists
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I. Overview

The renin-angiotensin-aldosterone system (RAAS) is the most important component in the homeostatic regulation of blood pressure. Excessive activity of the RAAS may lead to hypertension, as well as fluid and electrolyte disorders.[1,2] Renin catalyzes the conversion of angiotensinogen to angiotensin I. Angiotensin I is then cleaved to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II may also be generated through other pathways (angiotensin I convertase).[1] Angiotensin II can increase blood pressure by direct vasoconstriction, as well as through actions on the brain and autonomic nervous system.[1,2] In addition, angiotensin II stimulates aldosterone synthesis from the adrenal cortex, leading to sodium and water reabsorption. Angiotensin II exerts other detrimental effects, including ventricular hypertrophy, remodeling, and myocyte apoptosis.[1,2]

The angiotensin II receptor antagonists are approved for the treatment of diabetic nephropathy, heart failure, hypertension and post-myocardial infarction.[3-20] Since angiotensin II may be generated through other pathways that do not depend upon ACE, blockade of angiotensin II by ACE inhibitors is incomplete. Angiotensin II receptor antagonists block the angiotensin II receptor subtype AT_1, preventing the negative effects of angiotensin II, regardless of its origin. They do not appear to affect bradykinin and may be an option for patients who cannot tolerate ACE inhibitors.[19,20] The angiotensin II receptor antagonists are available as single entity products, as well as in combination with hydrochlorothiazide or chlorthalidone. Hydrochlorothiazide inhibits the reabsorption of sodium and chloride in the cortical thick ascending limb of the loop of Henle and the early distal tubules. This action leads to an increase in the urinary excretion of sodium and chloride. Telmisartan and olmesartan are also available in combination with amlodipine, a nondihydropyridine calcium-channel blocking agent, which is a potent vasodilator.[19,20]

The angiotensin II receptor antagonists that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All single entity products with the exception of azilsartan are available generically. Fixed-dose combination products are available in a generic formulation with the exception of azilsartan-chlorthalidone. This class was last reviewed in May 2022.

Table 1. Angiotensin II Receptor Antagonists Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Azilsartan	tablet	Edarbi®	none
Candesartan	tablet	Atacand®*	candesartan
Irbesartan	tablet	Avapro®*	irbesartan
Losartan	tablet	Cozaar®*	losartan
Olmesartan	tablet	Benicar®*	olmesartan
Telmisartan	tablet	Micardis®*	telmisartan
Valsartan	tablet	Diovan®*	valsartan
Combination Products			
Azilsartan and chlorthalidone	tablet	Edarbyclor®	none
Candesartan and hydrochlorothiazide	tablet	Atacand HCT®*	candesartan and hydrochlorothiazide
Irbesartan and hydrochlorothiazide	tablet	Avalide®*	irbesartan and hydrochlorothiazide
Losartan and hydrochlorothiazide	tablet	Hyzaar®*	losartan and hydrochlorothiazide
Olmesartan and amlodipine and hydrochlorothiazide	tablet	Tribenzor®*	olmesartan and amlodipine and hydrochlorothiazide

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Olmesartan and hydrochlorothiazide	tablet	Benicar HCT®*	olmesartan and hydrochlorothiazide
Telmisartan and amlodipine	tablet	N/A	telmisartan and amlodipine
Telmisartan and hydrochlorothiazide	tablet	Micardis HCT®*	telmisartan and hydrochlorothiazide
Valsartan and hydrochlorothiazide	tablet	Diovan HCT®*	valsartan and hydrochlorothiazide

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the angiotensin II receptor antagonists are summarized in Table 2.

Table 2. Treatment Guidelines Using the Angiotensin II Receptor Antagonists

Clinical Guideline	Recommendations
American Heart Association/American College of Cardiology/American College of Clinical Pharmacy/American Society for Preventive Cardiology/National Lipid Association/ Preventive Cardiovascular Nurses Association **Guideline for the Management of Patients With Chronic Coronary Disease (2023)**[21]	• In patients with chronic coronary disease (CCD), high-intensity statin therapy is recommended with the aim of achieving a ≥50% reduction in LDL-C levels to reduce the risk of major adverse cardiovascular events (MACE). • In patients in whom high-intensity statin therapy is contraindicated or not tolerated, moderate-intensity statin therapy is recommended with the aim of achieving a 30% to 49% reduction in LDL-C levels to reduce the risk of MACE. • In patients with CCD who are judged to be at very high risk and on maximally tolerated statin therapy with an LDL-C level ≥70 mg/dL, ezetimibe can be beneficial to further reduce the risk of MACE. • In patients with CCD who are judged to be at very high risk and who have an LDL-C level ≥70 mg/dL, or a non–high-density lipoprotein cholesterol (HDL-C) level ≥100 mg/dL, on maximally tolerated statin and ezetimibe, a PCSK9 monoclonal antibody can be beneficial to further reduce the risk of MACE. • In patients with CCD on maximally tolerated statin therapy with an LDL-C level <100 mg/dL and a persistent fasting triglyceride level of 150 to 499 mg/dL after addressing secondary causes, icosapent ethyl may be considered to further reduce the risk of MACE and cardiovascular death. • In patients with CCD who are not at very high risk and on maximally tolerated statin therapy with an LDL-C level ≥70 mg/dL, it may be reasonable to add ezetimibe to further reduce the risk of MACE. • In patients with CCD on maximally tolerated statin therapy who have an LDL-C level ≥70 mg/dL, and in whom ezetimibe and PCSK9 monoclonal antibody are deemed insufficient or not tolerated, it may be reasonable to add bempedoic acid or inclisiran (in place of PCSK9 monoclonal antibody) to further reduce LDL-C levels. • In patients with CCD receiving statin therapy, adding niacin, fenofibrate, or dietary supplements containing omega-3 fatty acids are not beneficial in reducing cardiovascular risk. • In adults with CCD, nonpharmacologic strategies are recommended as first-line therapy to lower BP in those with elevated BP (120-129/<80 mmHg). • In adults with CCD who have hypertension, a BP target of <130/<80 mmHg is recommended to reduce CVD events and all-cause death. • In adults with CCD and hypertension (systolic BP ≥130 and/or diastolic BP ≥80 mm Hg), in addition to nonpharmacological strategies, GDMT angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), or beta blockers are recommended as first-line therapy for compelling indications

Clinical Guideline	Recommendations
	(e.g., recent MI or angina), with additional antihypertensive medications (e.g., dihydropyridine calcium channel blockers [CCB], long-acting thiazide diuretics, and/or mineralocorticoid receptor antagonists) added as needed to optimize BP control. • In patients with CCD and no indication for oral anticoagulant therapy, low-dose aspirin 81 mg (75 to 100 mg) is recommended to reduce atherosclerotic events. • In patients with CCD treated with PCI, dual antiplatelet therapy (DAPT) consisting of aspirin and clopidogrel for 6 months post PCI followed by single antiplatelet therapy (SAPT) is indicated to reduce MACE and bleeding events.* • In select patients with CCD treated with PCI and a drug-eluting stent (DES) who have completed a 1- to 3-month course of DAPT, P2Y12 inhibitor monotherapy for at least 12 months is reasonable to reduce bleeding risk. • In patients with CCD who have had a previous MI and are at low bleeding risk, extended DAPT beyond 12 months for a period of up to 3 years may be reasonable to reduce MACE. • In patients with CCD and a previous history of MI without a history of stroke, transient ischemic attack (TIA), or ICH, vorapaxar may be added to aspirin therapy to reduce MACE. • In patients with CCD, the use of DAPT after CABG may be useful to reduce the incidence of saphenous vein graft occlusion. • In patients with CCD without recent ACS or a PCI-related indication for DAPT, the addition of clopidogrel to aspirin therapy is not useful to reduce MACE. • In patients with CCD and previous stroke, TIA, or ICH, vorapaxar should not be added to DAPT because of increased risk of major bleeding and ICH. • In patients with CCD and previous stroke, TIA, or ICH, prasugrel should not be used because of risk of significant or fatal bleeding. • In patients with CCD, chronic nonsteroidal anti-inflammatory drugs should not be used because of increased cardiovascular and bleeding complications. • In patients with CCD who have undergone elective PCI and who require oral anticoagulant therapy, DAPT for one to four weeks followed by clopidogrel alone for six months should be administered in addition to DOAC. • In patients with CCD who have undergone PCI and who require oral anticoagulant therapy, continuing aspirin in addition to clopidogrel for up to 1 month is reasonable if the patient has a high thrombotic risk and low bleeding risk. • In patients with CCD who require oral anticoagulation and have a low atherothrombotic risk, discontinuation of aspirin therapy with continuation of DOAC alone may be considered one year after PCI to reduce bleeding risk. • In patients with CCD who require oral anticoagulation, DOAC monotherapy may be considered if there is no acute indication for concomitant antiplatelet therapy. • In patients with CCD without an indication for therapeutic DOAC or DAPT and who are at high risk of recurrent ischemic events but low-to-moderate bleeding risk, the addition of low-dose rivaroxaban 2.5 mg twice daily to aspirin 81 mg daily is reasonable for long-term reduction of risk for MACE. • In patients with CCD on DAPT, the use of a PPI can be effective in reducing gastrointestinal bleeding risk. • In patients with CCD and LVEF ≤40% with or without previous MI, the use of beta-blocker therapy is recommended to reduce the risk of future MACE, including cardiovascular death. • In patients with CCD and LVEF<50%, the use of sustained release metoprolol succinate, carvedilol, or bisoprolol with titration to target doses is recommended in preference to other beta blockers. • In patients with CCD who were initiated on beta-blocker therapy for previous MI without a history of or current LVEF ≤50%, angina, arrhythmias, or uncontrolled hypertension, it may be reasonable to reassess the indication for long-term (>1

Clinical Guideline	Recommendations
	year) use of beta-blocker therapy for reducing MACE. • In patients with CCD without previous MI or LVEF ≤50%, the use of beta-blocker therapy is not beneficial in reducing MACE, in the absence of another primary indication for beta-blocker therapy. • In patients with CCD who also have hypertension, diabetes, LVEF ≤40%, or CKD, the use of ACE inhibitors, or ARBs if ACE inhibitor–intolerant, is recommended to reduce cardiovascular events. • In patients with CCD without hypertension, diabetes, or CKD and LVEF >40%, the use of ACE inhibitors or ARBs may be considered to reduce cardiovascular events. • In patients with CCD, the addition of colchicine for secondary prevention may be considered to reduce recurrent ASCVD events. • In patients with CCD, an annual influenza vaccination is recommended to reduce cardiovascular morbidity, cardiovascular death, and all-cause death. • In patients with CCD, coronavirus disease 2019 (COVID-19) vaccination is recommended per public health guidelines to reduce COVID-19 complications. • In patients with CCD, a pneumococcal vaccine is reasonable to reduce cardiovascular morbidity and mortality and all-cause death. • In patients with CCD and angina, antianginal therapy with either a beta blocker, CCB, or long-acting nitrate is recommended for relief of angina or equivalent symptoms. • In patients with CCD and angina who remain symptomatic after initial treatment, addition of a second antianginal agent from a different therapeutic class (beta blockers, CCB, long-acting nitrates) is recommended for relief of angina or equivalent symptoms. • In patients with CCD, ranolazine is recommended in patients who remain symptomatic despite treatment with beta blockers, CCB, or long-acting nitrate therapies. • In patients with CCD, sublingual nitroglycerin or nitroglycerin spray is recommended for immediate short-term relief of angina or equivalent symptoms. • In patients with CCD and normal LV function, the addition of ivabradine to standard anti-anginal therapy is potentially harmful. • In patients with CCD and lifestyle-limiting angina despite GDMT and with significant coronary artery stenoses amenable to revascularization, revascularization is recommended to improve symptoms. • In patients with CCD who have experienced SCAD, beta-blocker therapy may be reasonable to reduce the incidence of recurrent SCAD. • Women with CCD who are contemplating pregnancy or who are pregnant should not use ACE inhibitors, ARBs, direct renin inhibitors, angiotensin receptor-neprilysin inhibitors, or aldosterone antagonists during pregnancy to prevent harm to the fetus. • Women with CCD should not receive systemic postmenopausal hormone therapy because of a lack of benefit on MACE and mortality, and an increased risk of venous thromboembolism.
European Society of Cardiology: **Guidelines for the Diagnosis and Management of Chronic Coronary Syndromes (2019)**[22]	<u>Pharmacological management of stable coronary artery disease (CAD) patients</u> • The two aims of the pharmacological management of stable CAD patients are to obtain relief of symptoms and to prevent CV events. • Optimal medical treatment indicates at least one drug for angina/ischaemia relief plus drugs for event prevention. • It is recommended to educate patients about the disease, risk factors and treatment strategy. • It is indicated to review the patient's response soon after starting therapy. • Concomitant use of a proton pump inhibitor is recommended in patients receiving aspirin monotherapy, DAPT, or DOAC monotherapy who are at high risk of gastrointestinal bleeding.

Clinical Guideline	Recommendations

	• Lipid-lowering drugs: if goals are not met on maximum tolerated dose of a statin, consideration of combination therapy with ezetimibe or a PCSK9 inhibitor is recommended
	• ACE inhibitors should be considered in patients at a very high risk of cardiovascular adverse events
	• Angina/ischemia relief:
	  o Short-acting nitrates are recommended.
	  o First-line treatment is indicated with ß-blockers and/or calcium channel blockers to control heart rate and symptoms.
	  o Long-acting nitrates should be considered as a second-line treatment option when initial therapy with a beta-blocker and/or a non-DHP-calcium channel blocker is contraindicated, poorly tolerated, or inadequate in controlling angina symptoms
	  o Nicorandil, ranolazine, ivabradine, or trimetazidine should be considered as a second-line treatment to reduce angina frequency and improve exercise tolerance in subjects who cannot tolerate, have contraindications to, or whose symptoms are not adequately controlled by beta-blockers, CCBs, and long-acting nitrates.
	  o According to comorbidities/tolerance, it is indicated to use second-line therapies as first-line treatment in selected patients.
	  o In asymptomatic patients with large areas of ischaemia (>10%) ß-blockers should be considered.
	  o In patients with vasospastic angina, calcium channel blockers and nitrates should be considered and beta-blockers avoided.
	• Event prevention:
	  o Low-dose aspirin daily is recommended in all stable CAD patients.
	  o Clopidogrel is indicated as an alternative in case of aspirin intolerance.
	  o Statins are recommended in all stable CAD patients.
	  o It is recommended to use ACE inhibitors (or ARBs) if presence of other conditions (e.g., heart failure, hypertension or diabetes).
	
	<u>Treatment in patients with microvascular angina</u>
	• It is recommended that all patients receive secondary prevention medications including aspirin and statins.
	• ß-blockers are recommended as a first-line treatment.
	• Calcium antagonists are recommended if ß-blockers do not achieve sufficient symptomatic benefit or are not tolerated.
	• ACE inhibitors or nicorandil may be considered in patients with refractory symptoms.
	• Xanthine derivatives or nonpharmacological treatments such as neurostimulatory techniques may be considered in patients with symptoms refractory to the above listed drugs.
	
	<u>Stenting and peri-procedural antiplatelet strategies in stable CAD patients</u>
	• Drug-eluting stent (DES) is recommended in stable CAD patients undergoing stenting if there is no contraindication to prolonged dual antiplatelet therapy (DAPT).
	• Aspirin is recommended for elective stenting.
	• Clopidogrel is recommended for elective stenting.
	• Prasugrel or ticagrelor should be considered in patients with stent thrombosis on clopidogrel without treatment interruption.
	• GP IIb/IIIa antagonists should be considered for bailout situation only.
	• Platelet function testing or genetic testing may be considered in specific or high risk situations (e.g., prior history of stent thrombosis; compliance issue; suspicion of resistance; high bleeding risk) if results may change the treatment strategy.

Clinical Guideline	Recommendations
	• Prasugrel or ticagrelor may be considered in specific high risk situations of elective stenting (e.g., left main stenting, high risk of stent thrombosis, diabetes). • Pretreatment with clopidogrel (when coronary anatomy is not known) is not recommended. • Routine platelet function testing (clopidogrel and aspirin) to adjust antiplatelet therapy before or after elective stenting is not recommended. • Prasugrel or ticagrelor is not recommended in low risk elective stenting. • After uncomplicated PCI, early cessation (≤1 week) of aspirin, and continuation of dual therapy with oral anticoagulation therapy and clopidogrel should be considered if the risk of stent thrombosis is low • Triple therapy with aspirin, clopidogrel, and a DOAC for ≥1 month should be considered when the risk of stent thrombosis outweighs the bleeding risk, with a total of no more than six months <u>Follow-up of revascularized stable coronary artery disease patients</u> • It is recommended that all revascularized patients receive a secondary prevention and be scheduled for follow-up visit. • It is recommended to instruct patients before discharge about return to work and reuptake of full activities. Patients have to be advised to seek immediate medical contact if symptoms (re-) occur. • Single antiplatelet therapy, usually aspirin, is recommended indefinitely. • DAPT is indicated after bare metal stent (BMS) for at least one month. • DAPT is indicated for six to 12 months after second generation DES. • DAPT may be used for more than one year in patients at high ischemic risk (e.g., stent thrombosis, recurrent acute coronary syndrome on DAPT, post MI/diffuse CAD) and low bleeding risk. • DAPT for one to three months may be used after DES implantation in patients at high bleeding risk or with undeferrable surgery or concomitant anticoagulant treatment. <u>Antithrombotic therapy in patients with chronic coronary syndrome:</u> • Addition of a second antithrombotic drug to aspirin for long-term secondary prevention should be considered in patients with at least a moderately increased risk of ischemic events and without high bleeding risk • When oral anticoagulation is initiated in patients with AF, a DOAC is recommended in preference to VKA therapy.
American College of Physicians/ American College of Cardiology Foundation/ American Heart Association/ American Association for Thoracic Surgery/ Preventive Cardiovascular Nurses Association/ Society of Thoracic Surgeons: **Management of Stable Ischemic Heart Disease (2012)**[23]	<u>Medical therapy to prevent MI and death in patients with stable IHD</u> • Aspirin 75 to 162 mg daily should be continued indefinitely in the absence of contraindications. • Treatment with clopidogrel is a reasonable option when aspirin in contraindicated. • Dipyridamole should not be used as antiplatelet therapy. • Beta-blocker therapy should be initiated and continued for three years in all patients with normal left ventricular (LV) function following MI or acute coronary syndromes. • Metoprolol succinate, carvedilol, or bisoprolol should be used for all patients with systolic LV dysfunction (ejection fraction ≤40%) with heart failure or prior MI, unless contraindicated. • ACE inhibitors should be prescribed in all patients with stable IHD who also have hypertension, diabetes, LV systolic dysfunction (ejection fraction ≤40%), and/or chronic kidney disease, unless contraindicated. • Angiotensin-receptor blockers (ARBs) are recommended for patients with stable IHD who have hypertension, diabetes, LV systolic dysfunction, or chronic kidney disease and have indications for, but are intolerant of, ACE inhibitors. • Patients should receive an annual influenza vaccine.

Clinical Guideline	Recommendations
	Medical therapy for relief of symptoms in patients with stable IHD • Beta-blockers are recommended as initial therapy for relief of symptoms. • Calcium channel blockers or long-acting nitrates should be prescribed for relief of symptoms when β-blockers are contraindicated or cause unacceptable side effects. • Calcium channel blockers or long-acting nitrates, in combination with β-blockers, should be prescribed for relief of symptoms when initial treatment with β-blockers is unsuccessful. • Nitroglycerin or nitroglycerin spray should be used for immediate relief of angina. • Ranolazine is a fourth-line agent reserved for patients who have contraindications to, do not respond to, or cannot tolerate β-blockers, calcium-channel blockers, or long-acting nitrates.
American College of Cardiology Foundation/American Heart Association: **2014 American Heart Association/ American College of Cardiology Foundation Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes (2014)[24]**	Early hospital care- standard medical therapies • Supplemental oxygen should be administered to patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) with arterial oxygen saturation <90%, respiratory distress, or other high risk features of hypoxemia. • Anti-ischemic and analgesic medications o Nitrates ▪ Patients with NSTE-ACS with continuing ischemic pain should receive sublingual nitroglycerin (0.3 to 0.4 mg) every 5 minutes for up to three doses, after which an assessment should be made about the need for intravenous nitroglycerin. ▪ Intravenous nitroglycerin is indicated for patients with NSTE-ACS for the treatment of persistent ischemia, heart failure, or hypertension. ▪ Nitrates should not be administered to patients who recently received a phosphodiesterase inhibitor, especially within 24 hours of sildenafil or vardenafil, or within 48 hours of tadalafil. o Analgesic therapy ▪ In the absence of contraindications, it may be reasonable to administer morphine sulphate intravenously to patients with NSTE-ACE if there is continued ischemic chest pain despite treatment with maximally tolerated anti-ischemic medications. ▪ Nonsteroidal anti-inflammatory drugs (NSAIDs) (except aspirin) should not be initiated and should be discontinued during hospitalization due to the increased risk of major adverse cardiac event associated with their use o Beta-adrenergic blockers ▪ Oral β-blocker therapy should be initiated within the first 24 hours in patients who do not have any of the following: 1) signs of HF, 2) evidence of low-output state, 3) increased risk for cardiogenic shock, or 4) other contraindications to β-blockade (e.g., PR interval >0.24 second, second- or third-degree heart block without a cardiac pacemaker, active asthma, or reactive airway disease) ▪ In patients with concomitant NSTE-ACS, stabilized heart failure, and reduced systolic function, it is recommended to continue β-blocker therapy with one of the three drugs proven to reduce mortality in patients with heart failure: sustained-release metoprolol succinate, carvedilol, or bisoprolol. ▪ Patients with documented contraindications to β-blockers in the first 24 hours should be re-evaluated to determine subsequent eligibility. o Calcium channel blockers (CCBs) ▪ In patients with NSTE-ACS, continuing or frequently recurring ischemia, and a contraindication to β-blockers, a nondihydropyridine CCB (e.g., verapamil or diltiazem) should be given as initial therapy in

Clinical Guideline	Recommendations
	the absence of clinically significant LV dysfunction, increased risk for cardiogenic shock, PR interval >0.24 seconds, or second or third degree atrioventricular block without a cardiac pacemaker. ▪ Oral nondihydropyridine calcium antagonists are recommended in patients with NSTE-ACS who have recurrent ischemia in the absence of contraindications, after appropriate use of β-blockers and nitrates. ▪ CCBs are recommended for ischemic symptoms when β-blockers are not successful, are contraindicated, or cause unacceptable side effects. ▪ Long-acting CCBs and nitrates are recommended in patients with coronary artery spasm. ▪ Immediate-release nifedipine should not be administered to patients with NSTE-ACS in the absence of β-blocker therapy. o Other anti-ischemic interventions ▪ Ranolazine is currently indicated for treatment of chronic angina; however, it may also improve outcomes in NSTE-ACS patients due to a reduction in recurrent ischemia. o Cholesterol management ▪ High-intensity statin therapy should be initiated or continued in all patients with NSTE-ACS and no contraindications to its use. Treatment with statins reduces the rate of recurrent MI, coronary heart disease mortality, need for myocardial revascularization, and stroke. ▪ It is reasonable to obtain a fasting lipid profile in patients with NSTE-ACS, preferably within 24 hours of presentation. • Inhibitors of renin-angiotensin-aldosterone system o ACE inhibitors should be started and continued indefinitely in all patients with LVEF <0.40 and in those with hypertension, diabetes mellitus, or stable CKD, unless contraindicated. o ARBs are recommended in patients with heart failure or myocardial infarction with LVEF <0.40 who are ACE inhibitor intolerant. o Aldosterone-blockade is recommended in patients post-MI without significant renal dysfunction (creatinine >2.5 mg/dL in men or >2.0 mg/dL in women) or hyperkalemia (K >5.0 mEq/L) who are receiving therapeutic doses of ACE inhibitor and β-blocker and have a LVEF <0.40, diabetes mellitus, or heart failure. • Initial antiplatelet/anticoagulant therapy in patients with definite or likely NSTE-ACS treated with an initial invasive or ischemia-guided strategy o Non-enteric coated, chewable aspirin (162 to 325 mg) should be given to all patients with NSTE-ACS without contraindications as soon as possible after presentation, and a maintenance dose of aspirin (81 to 162 mg/day) should be continued indefinitely. o In patients who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance, a loading dose of clopidogrel followed by a daily maintenance dose should be administered. o A $P2Y_{12}$ receptor inhibitor (clopidogrel or ticagrelor) in addition to aspirin should be administered for up to 12 months to all patients with NSTE-ACS without contraindications who are treated with an early invasive or ischemia-guided strategy. Options include: ▪ Clopidogrel: 300 or 600 mg loading dose, then 75 mg daily. ▪ Ticagrelor: 180 mg loading dose, then 90 mg twice daily. ▪ It is reasonable to use ticagrelor in preference to clopidogrel for $P2Y_{12}$ treatment in patients with NSTE-ACS who undergo an early invasive or ischemia-guided strategy. ▪ In patients with NSTE-ACS treated with an early invasive strategy and dual antiplatelet therapy (DAPT) with intermediate/high-risk features (e.g., positive troponin), a GP IIb/IIIa inhibitor may be considered as part of initial antiplatelet therapy. Preferred options are eptifibatide or

Clinical Guideline	Recommendations
	tirofiban. <u>Percutaneous coronary intervention (PCI)- Antiplatelet and anticoagulant therapy</u> • Antiplatelet agents o Patients already taking daily aspirin before PCI should take 81 to 325 mg non-enteric coated aspirin before PCI o Patients not on aspirin therapy should be given non-enteric coated aspirin 325 mg as soon as possible before PCI. o After PCI, aspirin should be continued indefinitely. o A loading dose of a $P2Y_{12}$ inhibitor should be given before the procedure in patients undergoing PCI with stenting. Options include clopidogrel 600 mg, prasugrel 60 mg, or ticagrelor 180 mg. o In patients with NSTE-ACS and high-risk features (e.g., elevated troponin) not adequately pretreated with clopidogrel or ticagrelor, it is useful to administer a GP IIb/IIIa inhibitor (abciximab, double-bolus eptifibatide, or high-dose bolus tirofiban) at the time of PCI. o In patients receiving a stent (bare metal or drug eluting) during PCI, $P2Y_{12}$ inhibitor therapy should be given for at least 12 months. Options include clopidogrel 75 mg daily, prasugrel 10 mg daily, or ticagrelor 90 mg twice daily. • Anticoagulant therapy o An anticoagulant should be administered to patients with NSTE-ACS undergoing PCI to reduce the risk of intracoronary and catheter thrombus formation. o Intravenous unfractionated heparin (UFH) is useful in patients with NSTE-ACS undergoing PCI. o Bivalirudin is useful as an anticoagulant with or without prior treatment with UFH. o An additional dose of 0.3 mg/kg intravenous enoxaparin should be administered at the time of PCI to patients with NSTE-ACS who have received fewer than two therapeutic subcutaneous doses or received the last subcutaneous enoxaparin dose eight to 12 hours before PCI. o If PCI is performed while the patient is on fondaparinux, an additional 85 IU/kg of UFH should be given intravenously immediately before PCI because of the risk of catheter thrombosis (60 IU/kg IV if a GP IIb/IIIa inhibitor used with UFH dosing based on the target-activated clotting time). o Anticoagulant therapy should be discontinued after PCI unless there is a compelling reason to continue. • Timing of CABG in relation to use of antiplatelet agents o Non-enteric coated aspirin (81 to 325 mg daily) should be administered preoperatively to patients undergoing CABG. o In patients referred for elective CABG, clopidogrel and ticagrelor should be discontinued for at least five days before surgery and prasugrel for at least seven days before surgery. o In patients referred for urgent CABG, clopidogrel and ticagrelor should be discontinued for at least 24 hours to reduce major bleeding. o In patients referred for CABG, short-acting intravenous GP IIb/IIIa inhibitors (eptifibatide or tirofiban) should be discontinued for at least 2 to 4 hours before surgery and abciximab for at least 12 hours before to limit blood loss and transfusion. <u>Late hospital care, hospital discharge, and posthospital discharge care</u> • Medications at discharge o Medications required in the hospital to control ischemia should be continued after hospital discharge in patients with NSTE-ACS who do not undergo coronary revascularization, patients with incomplete or unsuccessful

Clinical Guideline	Recommendations
	revascularization, and patients with recurrent symptoms after revascularization. Titration of the doses may be required. o All patients who are post–NSTE-ACS should be given sublingual or spray nitroglycerin with verbal and written instructions for its use. o Before hospital discharge, patients with NSTE-ACS should be informed about symptoms of worsening myocardial ischemia and MI and should be given verbal and written instructions about how and when to seek emergency care for such symptoms. o Before hospital discharge, patients who are post–NSTE-ACS and/or designated responsible caregivers should be provided with easily understood and culturally sensitive verbal and written instructions about medication type, purpose, dose, frequency, side effects, and duration of use. o For patients who are post–NSTE-ACS and have initial angina lasting more than one minute, nitroglycerin (one dose sublingual or spray) is recommended if angina does not subside within three to five minutes; call 9-1-1 immediately to access emergency medical services. o If the pattern or severity of angina changes, suggesting worsening myocardial ischemia (e.g., pain is more frequent or severe or is precipitated by less effort or occurs at rest), patients should contact their clinician without delay to assess the need for additional treatment or testing. o Before discharge, patients should be educated about modification of cardiovascular risk factors. • Late hospital and post-hospital oral antiplatelet therapy o Aspirin should be continued indefinitely. The dose should be 81 mg daily in patients treated with ticagrelor and 81 to 325 mg daily in all other patients. o In addition to aspirin, a $P2Y_{12}$ inhibitor (either clopidogrel or ticagrelor) should be continued for up to 12 months in all patients with NSTE-ACS without contraindications who are treated with an ischemia-guided strategy. o In patients receiving a stent (bare-metal stent or DES) during PCI for NSTE-ACS, P2Y12 inhibitor therapy should be given for at least 12 months. • Combined oral anticoagulant therapy and antiplatelet therapy in patients with NSTE-ACS o The duration of triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a $P2Y_{12}$ receptor inhibitor in patients with NSTE-ACS should be minimized to the extent possible to limit the risk of bleeding. o Proton pump inhibitors should be prescribed in patients with NSTE-ACS with a history of gastrointestinal bleeding who require triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a $P2Y_{12}$ receptor inhibitor.
European Society of Cardiology: **Guidelines for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation (2020)**[25]	<u>Pharmacological treatment of ischemia</u> • Sublingual or intravenous nitrates and early initiation of β-blocker treatment is recommended in patients with ongoing ischemic symptoms and without contraindications. • Continuation of chronic β-blocker therapy is recommended unless the patient is in overt heart failure • Sublingual or intravenous nitrates are recommended to relieve angina; intravenous treatment is recommended in patients with recurrent angina, uncontrolled hypertension, or signs of heart failure. • In patients with suspected/confirmed vasospastic angina, calcium channel blockers, and nitrates should be considered and β-blockers avoided. <u>Recommendations for platelet inhibition in non-ST-elevation acute coronary syndromes</u> • Aspirin is recommended for all patients without contraindications at an initial oral loading dose of 150 to 300 mg (in aspirin-naïve patients) and a maintenance dose of 75 to 100 mg/day long-term regardless of treatment strategy.

Clinical Guideline	Recommendations

	• A $P2Y_{12}$ inhibitor is recommended, in addition to aspirin, for 12 months unless there are contraindications such as excessive risks of bleeds.
	  ○ Ticagrelor (180 mg loading dose, 90 mg twice daily) is recommended, in the absence of contraindication, for all patients at moderate-to-high risk of ischemic events (e.g., elevated cardiac troponins), regardless of initial treatment strategy and including those pretreated with clopidogrel (which should be discontinued when ticagrelor is started).
	  ○ Prasugrel (60 mg loading dose, 10 mg daily dose) is recommended in patients who are proceeding to PCI if no contraindication. Prasugrel should be considered in preference to ticagrelor in NSTE-ACS patients who proceed to PCI.
	  ○ Clopidogrel (300 to 600 mg loading dose, 75 mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel or who require oral anticoagulation.
	• $P2Y_{12}$ inhibitor administration for a shorter duration of three to six months after DES implantation may be considered in patients deemed at high bleeding risk.
	• Pre-treatment with a $P2Y_{12}$ inhibitor may be considered in patients with NSTE-ACS who are not planned to undergo an early invasive strategy.
	• It is not recommended to administer routine pre-treatment with a $P2Y_{12}$ inhibitor in patients in whom coronary anatomy is not known.
	• It is not recommended to administer prasugrel in patients whom coronary anatomy is not known.
	• GPIIb/IIIa inhibitors during PCI should be considered for bailout situations or thrombotic complications.
	• Cangrelor may be considered in $P2Y_{12}$ inhibitor-naïve patients undergoing PCI.
	• It is not recommended to administer GPIIb/IIIa inhibitors in patients whom coronary anatomy is not known.
	• $P2Y_{12}$ inhibitor administration in addition to aspirin beyond one year may be considered after careful assessment of the ischemic and bleeding risks of the patient.
	
	<u>Recommendations for anticoagulation in non-ST-elevation acute coronary syndromes</u>
	• Parenteral anticoagulation is recommended at the time of diagnosis according to both ischemic and bleeding risks.
	• Fondaparinux is recommended as having the most favorable efficacy-safety profile regardless of the management strategy.
	• Bivalirudin is recommended as an alternative to UFH plus GPIIb/IIIa inhibitors during PCI.
	• UFH is recommended in patients undergoing PCI who did not receive any anticoagulant.
	• In patients on fondaparinux undergoing PCI, a single intravenous bolus of UFH is recommended during the procedure.
	• Enoxaparin or UFH are recommended when fondaparinux is not available.
	• Enoxaparin should be considered as an anticoagulant for PCI in patients pretreated for PCI with subcutaneous enoxaparin.
	• Additional activated clotting time-guided intravenous boluses of UFH during PCI may be considered following initial UFH treatment.
	• Discontinuation of anticoagulation should be considered after PCI, unless otherwise indicated.
	• Crossover between UFH and LMWH is not recommended.
	• In NSTEMI patients with no prior stroke/TIA and at high ischemic risk as well as low bleeding risk receiving aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily for approximately one year) may be considered after discontinuation of parenteral anticoagulation.

Clinical Guideline	Recommendations
	Recommendations for combining antiplatelet agents and anticoagulants in non-ST-elevation acute coronary syndrome patients requiring chronic oral anticoagulation • In patients with a firm indication for oral anticoagulation (e.g., atrial fibrillation with a $CHADS_2$-VASc score ≥2, recent VTE, mechanical valve prosthesis), oral anticoagulation is recommended in addition to antiplatelet therapy. • An early invasive coronary angiography (within 24 hours) should be considered in moderate- to high-risk patients, irrespective of oral anticoagulant exposure, to expedite treatment allocation (medical vs PCI vs CABG) and to determine optimal antithrombotic regimen. • Initial dual antiplatelet therapy with aspirin plus a $P2Y_{12}$ inhibitor in addition to oral anticoagulation before coronary angiography is not recommended. • During PCI, additional parenteral anticoagulation is recommended, irrespective of the timing of the last dose of all non-vitamin K antagonist oral anticoagulants (NOACs) and if INR is <2.5 in VKA-treated patients. • Uninterrupted therapeutic anticoagulation with VKA or NOACs should be considered during the periprocedural phase. • Periprocedural DAPT administration consisting of aspirin and clopidogrel up to one week is recommended • Discontinuation of antiplatelet treatment in patients treated with an oral anticoagulant is recommended after 12 months • Following coronary stenting, dual (oral) antiplatelet therapy (DAPT) including new $P2Y_{12}$ inhibitors should be considered as an alternative to triple therapy for patients with non-ST-elevation acute coronary syndromes and atrial fibrillation with a $CHADS_2$-VASc score of 1 (in males) or 2 (in females). • If at low bleeding risk (HAS-BLED ≤2), triple therapy with oral anticoagulant, aspirin, and clopidogrel should be considered for six months, followed by oral anticoagulant and aspirin or clopidogrel continued up to 12 months. • If at high bleeding risk (HAS-BLED ≥3), triple therapy with oral anticoagulant, aspirin, and clopidogrel should be considered for one month, followed by oral anticoagulant and aspirin or clopidogrel continued up to 12 months irrespective of the stent type. • Dual therapy with oral anticoagulant and clopidogrel may be considered as an alternative to triple antithrombotic therapy in selected patients (HAS-BLED ≥3 and low risk of stent thrombosis). • The use of ticagrelor or prasugrel as part of triple therapy is not recommended. • In medically managed patients, one antiplatelet agent in addition to oral anticoagulant should be considered for up to one year. Recommendations for post-interventional and maintenance treatment • In patients with NSTE-ACS with coronary stent implantation, DAPT with a $P2Y_{12}$ inhibitor on top of aspirin is recommended for 12 months unless there are contraindications such as excessive risk of bleeding. • Adding a second anti-thrombotic agent to aspirin for extended long-term secondary prevention should be considered in patients with a moderate to high risk of ischemic events and without increased risk of major bleeding. • After stent implantation with high risk of bleeding, discontinuation of $P2Y_{12}$ inhibitor therapy after three months should be considered • After stent implantation in patients undergoing DAPT, stopping aspirin after three to six months should be considered, depending on balance between ischemic and bleeding risk. • De-escalation of $P2Y_{12}$ inhibitor treatment may be considered as an alternative DAPT strategy, especially for ACS patients deemed unsuitable for potent platelet inhibition.
American College of Cardiology/American	Routine medical therapies: β-blockers • Oral β-blockers should be initiated within the first 24 hours in patients with an

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Heart Association: **Guideline for the Management of ST-Elevation Myocardial Infarction (2013)**[26]	ST-segment elevation myocardial infarction (STEMI) who do not have any of the following: 1) signs of heart failure, 2) evidence of a low-output state, 3) increased risk of cardiogenic shock, 4) other contraindications to use of oral β-blockers (e.g., PR interval >24 seconds, second or third degree heart block, active asthma, reactive airway disease). • β-blockers should be continued during and after hospitalization for all patients with STEMI and with no contraindications to their use. • Patients with initial contraindications to the use of β-blockers in the first 24 hours after STEMI should be re-evaluated to determine their subsequent eligibility. • It is reasonable to administer intravenous β-blockers at the time of presentation to patients with STEMI and no contraindications to their use who are hypertensive or have ongoing ischemia. <u>Routine medical therapies: renin-angiotensin-aldosterone system inhibitors</u> • An ACE inhibitor should be administered within the first 24 hours to all patients with ST-segment elevation myocardial infarction with anterior location, heart failure, or ejection fraction ≤40%, unless contraindicated. • An ARB should be given to patients who have indications for but are intolerant of ACE inhibitors. • ACE inhibitors are reasonable for all patients with no contraindications to their use. • An aldosterone antagonist should be given to patients with STEMI and no contraindications who are already receiving an ACE inhibitor and β-blocker and who have an EF ≤40% and either symptomatic heart failure or diabetes. <u>Routine medical therapies: Lipid management</u> • High-intensity statin therapy should be initiated or continued in all patients with STEMI and no contraindications to its use. • It is reasonable to obtain a fasting lipid profile in patients with STEMI, preferably within 24 hours of presentation.
European Society of Cardiology: **Management of Acute Myocardial Infarction in Patients Presenting with ST-segment Elevation (2017)**[27]	<u>Routine therapies in the acute, subacute and long term phase of ST-elevation myocardial infarction (STEMI)</u> • Antiplatelet therapy with low dose aspirin (75 to 100 mg) is indicated indefinitely after STEMI. • Dual antiplatelet therapy with a combination of aspirin and prasugrel or aspirin and ticagrelor is recommended for 12 months after percutaneous coronary intervention (PCI), unless there are contraindications such as excessive risk of bleeding. • A proton pump inhibitor (PPI) in combination with dual antiplatelet therapy is recommended in patients at high risk of gastrointestinal bleeding. • In patients with an indication for oral anticoagulation, oral anticoagulants are indicated in addition to antiplatelet therapy. • In patients who are at high risk of severe bleeding complications, discontinuation of $P2Y_{12}$ inhibitor therapy after six months should be considered. • In STEMI patients with stent implantation and an indication for oral anticoagulation, triple therapy (oral anticoagulant, aspirin, and clopidogrel) should be considered for one to six months (according a balance between the estimated risk of recurrent coronary events and bleeding). • In patients with left ventricular thrombus, anticoagulation should be instituted for a minimum of six months, guided by repeated imaging. • In selected patients who receive aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily) may be considered if the patient is at low bleeding risk. • Dual antiplatelet therapy should be used up to one year in patients with STEMI who did not receive a stent unless there are contraindications such as excessive risk of bleeding.

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	• In high ischemic-risk patients (age ≥50 years, and at least one of the following risk factors: age ≥65 years, diabetes mellitus on medication, prior spontaneous MAI, multivessel CAD, or chronic renal dysfunction with eGFR <60 mL/min) who have tolerated dual antiplatelet therapy without a bleeding complication, treatment with dual antiplatelet therapy in the form of ticagrelor 60 mg twice a day on top of aspirin for longer than 12 months may be considered for up to three years. • The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with aspirin and oral anticoagulation. • Oral treatment with β-blockers should be considered during hospital stay and continued thereafter in all patients without contraindications. • Oral treatment with β-blockers is indicated in patients with heart failure or left ventricular dysfunction, LVEF ≤40% unless contraindicated. • Intravenous β-blockers must be avoided in patients with hypotension or acute heart failure or AV block or severe bradycardia. • Intravenous β-blockers should be considered at the time of presentation in patients undergoing primary PCI without contraindications, with high blood pressure, tachycardia, and no signs of heart failure. • A fasting lipid profile must be obtained in all STEMI patients, as soon as possible after presentation. • It is recommended to initiate or continue high dose statins early after admission in all STEMI patients without contraindication or history of intolerance, regardless of initial cholesterol values and maintain it long-term. • An LDL-C goal of <1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline LDL-C is between 1.8 to 3.5 mmol/L (70 to 135 mg/dL) is recommended. • In patients with LDL-C >1.8 mmol/L (>70 mg/dL) despite a maximally tolerated statin dose who remain at high risk, further therapy to reduce LDL-C should be considered. • ACE inhibitors are indicated starting within the first 24 hours of STEMI in patients with evidence of heart failure, LV systolic dysfunction, diabetes or an anterior infarct. • An ARB, preferably valsartan, is an alternative to ACE inhibitors in patients with heart failure or LV systolic dysfunction, particularly those who are intolerant to ACE inhibitors. • ACE inhibitors should be considered in all patients in the absence of contraindications. • Aldosterone antagonists, e.g. eplerenone, are indicated in patients with an ejection fraction ≤40% and heart failure or diabetes, provided no renal failure or hyperkalemia.
American College of Cardiology/ American Heart Association: **Guideline on the Primary Prevention of Cardiovascular Disease (2019)**[28]	Top 10 messages for the primary prevention of cardiovascular disease • The most important way to prevent atherosclerotic vascular disease, heart failure, and atrial fibrillation is to promote a healthy lifestyle throughout life. • A team-based care approach is an effective strategy for the prevention of cardiovascular disease. Clinicians should evaluate the social determinants of health that affect individuals to inform treatment decisions. • Adults who are 40 to 75 years of age and are being evaluated for cardiovascular disease prevention should undergo 10-year atherosclerotic cardiovascular disease (ASCVD) risk estimation and have a clinician–patient risk discussion before starting on pharmacological therapy, such as antihypertensive therapy, a statin, or aspirin. In addition, assessing for other risk-enhancing factors can help guide decisions about preventive interventions in select individuals, as can coronary artery calcium scanning. • All adults should consume a healthy diet that emphasizes the intake of vegetables, fruits, nuts, whole grains, lean vegetable or animal protein, and fish

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	and minimizes the intake of trans fats, processed meats, refined carbohydrates, and sweetened beverages. For adults with overweight and obesity, counseling and caloric restriction are recommended for achieving and maintaining weight loss. • Adults should engage in at least 150 minutes per week of accumulated moderate-intensity physical activity or 75 minutes per week of vigorous-intensity physical activity. • For adults with type 2 diabetes mellitus, lifestyle changes, such as improving dietary habits and achieving exercise recommendations, are crucial. If medication is indicated, metformin is first-line therapy, followed by consideration of a sodium-glucose cotransporter 2 inhibitor or a glucagon-like peptide-1 receptor agonist. • All adults should be assessed at every healthcare visit for tobacco use, and those who use tobacco should be assisted and strongly advised to quit. • Aspirin should be used infrequently in the routine primary prevention of ASCVD because of lack of net benefit. • Statin therapy is first-line treatment for primary prevention of ASCVD in patients with elevated low-density lipoprotein cholesterol levels (≥190 mg/dL), those with diabetes mellitus, who are 40 to 75 years of age, and those determined to be at sufficient ASCVD risk after a clinician–patient risk discussion. • Nonpharmacological interventions are recommended for all adults with elevated blood pressure or hypertension. For those requiring pharmacological therapy, the target blood pressure should generally be <130/80 mm Hg. <u>Adults with Type 2 Diabetes Mellitus</u> • For all adults with T2DM, a tailored nutrition plan focusing on a heart-healthy dietary pattern is recommended to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors. • Adults with T2DM should perform at least 150 minutes per week of moderate-intensity physical activity or 75 minutes of vigorous-intensity physical activity to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors. • For adults with T2DM, it is reasonable to initiate metformin as first-line therapy along with lifestyle therapies at the time of diagnosis to improve glycemic control and reduce ASCVD risk. • For adults with T2DM and additional ASCVD risk factors who require glucose-lowering therapy despite initial lifestyle modifications and metformin, it may be reasonable to initiate a sodium-glucose cotransporter 2 (SGLT-2) inhibitor or a glucagon-like peptide-1 receptor (GLP-1R) agonist to improve glycemic control and reduce CVD risk. <u>Adults with high blood cholesterol</u> • In adults at intermediate risk (≥7.5% to <20% 10-year ASCVD risk), statin therapy reduces risk of ASCVD, and in the context of a risk discussion, if a decision is made for statin therapy, a moderate-intensity statin should be recommended. • In intermediate risk (≥7.5% to <20% 10-year ASCVD risk) patients, LDL-C levels should be reduced by 30% or more, and for optimal ASCVD risk reduction, especially in patients at high risk (≥20% 10-year ASCVD risk), levels should be reduced by 50% or more. • In adults 40 to 75 years of age with diabetes, regardless of estimated 10-year ASCVD risk, moderate-intensity statin therapy is indicated. • In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL (≥4.9 mmol/L) or higher, maximally tolerated statin therapy is recommended. • In adults with diabetes mellitus who have multiple ASCVD risk factors, it is

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	reasonable to prescribe high-intensity statin therapy with the aim to reduce LDL-C levels by 50% or more.
	• In intermediate-risk (≥7.5% to <20% 10-year ASCVD risk) adults, risk-enhancing factors favor initiation or intensification of statin therapy.
	• In intermediate-risk (≥7.5% to <20% 10-year ASCVD risk) adults or selected borderline-risk (5% to <7.5% 10-year ASCVD risk) adults in whom a coronary artery calcium score is measured for the purpose of making a treatment decision, AND
	  o If the coronary artery calcium score is zero, it is reasonable to withhold statin therapy and reassess in five to 10 years, as long as higher-risk conditions are absent (e.g., diabetes, family history of premature CHD, cigarette smoking);
	  o If coronary artery calcium score is one to 99, it is reasonable to initiate statin therapy for patients ≥55 years of age;
	  o If coronary artery calcium score is 100 or higher or in the 75th percentile or higher, it is reasonable to initiate statin therapy.
	• In patients at borderline risk (5% to <7.5% 10-year ASCVD risk), in risk discussion, the presence of risk-enhancing factors may justify initiation of moderate-intensity statin therapy.
	
	<u>Adults with high blood pressure or hypertension</u>
	• In adults with elevated blood pressure (BP) or hypertension, including those requiring antihypertensive medications nonpharmacological interventions are recommended to reduce BP. These include:
	  o weight loss;
	  o a heart-healthy dietary pattern;
	  o sodium reduction;
	  o dietary potassium supplementation;
	  o increased physical activity with a structured exercise program; and
	  o limited alcohol.
	• In adults with an estimated 10-year ASCVD risk (ACC/AHA pooled cohort equations to estimate 10-year risk of ASCVD) of 10% or higher and an average systolic BP (SBP) of 130 mm Hg or higher or an average diastolic BP (DBP) of 80 mm Hg or higher, use of BP-lowering medications is recommended for primary prevention of CVD.
	• In adults with confirmed hypertension and a 10-year ASCVD event risk of 10% or higher, a BP target of less than 130/80 mm Hg is recommended.
	• In adults with hypertension and chronic kidney disease, treatment to a BP goal of less than 130/80 mm Hg is recommended.
	• In adults with T2DM and hypertension, antihypertensive drug treatment should be initiated at a BP of 130/80 mm Hg or higher, with a treatment goal of less than 130/80 mm Hg.
	• In adults with an estimated 10-year ASCVD risk <10% and an SBP of 140 mm Hg or higher or a DBP of 90 mm Hg or higher, initiation and use of BP-lowering medication are recommended.
	• In adults with confirmed hypertension without additional markers of increased ASCVD risk, a BP target of less than 130/80 mm Hg may be reasonable.
	
	<u>Recommendations for treatment of tobacco use</u>
	• All adults should be assessed at every healthcare visit for tobacco use and their tobacco use status recorded as a vital sign to facilitate tobacco cessation.
	• To achieve tobacco abstinence, all adults who use tobacco should be firmly advised to quit.
	• In adults who use tobacco, a combination of behavioral interventions plus pharmacotherapy is recommended to maximize quit rates.

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	• In adults who use tobacco, tobacco abstinence is recommended to reduce ASCVD risk. • To facilitate tobacco cessation, it is reasonable to dedicate trained staff to tobacco treatment in every healthcare system. • All adults and adolescents should avoid secondhand smoke exposure to reduce ASCVD risk. <u>Recommendations for aspirin use</u> • Low-dose aspirin (75 to 100 mg orally daily) might be considered for the primary prevention of ASCVD among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk. • Low-dose aspirin (75 to 100 mg orally daily) should not be administered on a routine basis for the primary prevention of ASCVD among adults >70 years of age. • Low-dose aspirin (75 to 100 mg orally daily) should not be administered for the primary prevention of ASCVD among adults of any age who are at increased risk of bleeding.
American Heart Association/American College of Cardiology/ Heart Failure Society of America: **2022 AHA/ACC /HFSA Guideline for the Management of Heart Failure (2022)[29]**	<u>Treatment of Stage A heart failure (HF)</u> • Hypertension should be controlled in accordance with guideline-directed medication therapy for hypertension to prevent symptomatic HF. (LoE: A) • In patients with type 2 diabetes and either established CVD or at high cardiovascular risk, SGLT-2 inhibitors should be used to prevent hospitalizations for HF. (LoE: A) • In the general population, healthy lifestyle habits such as regular physical activity, maintaining normal weight, healthy dietary patterns, and avoiding smoking are helpful to reduce future risk of HF. (LoE: B) • Patients at risk of developing HF, natriuretic peptide biomarker-based screening followed by team-based care, including a cardiovascular specialist optimizing therapy, can be useful to prevent the development of LV dysfunction (systolic or diastolic) or new-onset HF. (LoE: B) <u>Treatment of Stage B heart failure</u> • In patients with LVEF≤40%, ACE inhibitors should be used to prevent HF and reduce mortality. (LoE: A) • In patients with a recent or remote history of MI or ACS, statins should be used to prevent symptomatic HF and adverse cardiovascular events. (LoE: A) • In patients with a recent MI and LVEF≤40% who are intolerant to ACE inhibitors, ARB should be used to prevent symptomatic HF and reduce mortality. (LoE: B) • In patients with a recent or remote history of MI or ACS and LVEF≤40%, evidence-based beta blockers should be used to reduce mortality. (LoE: B) • In patients who are at least 40 days post-MI with LVEF ≤30% and NYHA class I symptoms while receiving guideline-directed medication therapy and have reasonable expectation of meaningful survival for greater than one year, an implantable cardioverter-defibrillator is recommended for primary prevention of sudden cardiac death to reduce total mortality. (LoE: B) • In patients with LVEF ≤40%, beta blockers should be used to prevent symptomatic HF. (LoE: C) • In patients with LVEF ≤50%, thiazolidinediones should not be used because they increase the risk of HF, including hospitalizations. (LoE: B) • In patients with LVEF ≤50%, nondihydropyridine calcium channel blockers with negative inotropic effects may be harmful. (LoE: C) <u>Treatment for Stage C Heart Failure with Reduced Ejection Fraction (HFrEF)</u>

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	• For patients with stage C HF, avoiding excessive sodium intake is reasonable to reduce congestive symptoms. (LoE: C) • In patients with HF who have fluid retention, diuretics are recommended to relieve congestion, improve symptoms, and prevent worsening HF. (LoE: B) • For patients with HF and congestive symptoms, addition of a thiazide (e.g., metolazone) to treatment with a loop diuretic should be reserved for patients who do not respond to moderate or high dose loop diuretics to minimize electrolyte abnormalities. (LoE: B) • In patients with HFrEF and NYHA class II to III symptoms, the use of an ARNI is recommended to reduce morbidity and mortality. (LoE: A) • In patients with previous or current symptoms of chronic HFrEF, the use of an ACE inhibitor is beneficial to reduce morbidity and mortality when the use of an ARNI is not feasible. (LoE: A) • In patients with previous or current symptoms of chronic HFrEF, who are intolerant to an ACE inhibitor because of cough or angioedema, and when the use of an ARNI is not feasible, the use of an ARB is recommended to reduce morbidity and mortality. (LoE: A) • In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality. (LoE: B) • ARNIs should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor. (LoE: B) • ARNI or ACE inhibitors should not be administered in patients with a history of angioedema. (LoE: C) • In patients with HFrEF, with current or previous symptoms, use of one of the three β-blockers proven to reduce mortality (e.g., bisoprolol, carvedilol, sustained-release metoprolol succinate) is recommended to reduce mortality and hospitalizations. (LoE: A) • In patients with HFrEF and NYHA class II to IV symptoms, a mineralocorticoid receptor antagonist (spironolactone or eplerenone) is recommended to reduce morbidity and mortality, if eGFR is >30 mL/min/1.73 m^2 and serum potassium is <5.0 mEq/L. Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely followed thereafter to minimize risk of hyperkalemia and renal insufficiency. (LoE: A) • In patients taking a mineralocorticoid receptor antagonist whose serum potassium cannot be maintained at <5.5 mEq/L, mineralocorticoid receptor antagonist should be discontinued to avoid life threatening hyperkalemia. (LoE: B) • In patients with symptomatic chronic HFrEF, SGLT-2 an inhibitor is recommended to reduce hospitalization for HF and cardiovascular mortality, irrespective of the presence of type 2 diabetes. (LoE: A) • The combination of hydralazine and isosorbide dinitrate is recommended to improve symptoms and reduce morbidity and mortality for patients self-identified as African Americans with NYHA class III to IV HFrEF receiving optimal therapy. (LoE: A) • In patients with current or previous symptomatic HFrEF who cannot be given first-line agents, such as an ARNI, ACE inhibitor or ARB because of drug intolerance or renal insufficiency, a combination of hydralazine and isosorbide dinitrate might be considered to reduce morbidity and mortality. (LoE: C) • In patients with HF class II to IV symptoms, omega-3 polyunsaturated fatty acid supplementation may be reasonable to use as adjunctive therapy to reduce mortality and cardiovascular hospitalizations. (LoE: B) • In patients with chronic HFrEF without specific indication (e.g., venous thromboembolism, atrial fibrillation, a previous thromboembolic event, or a cardioembolic source, anticoagulation is not recommended. (LoE: B) • Dihydropyridine and non-dihydropyridine calcium channel blockers are not

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	recommended for patients with HFrEF. (LoE: A) • In patients with HFrEF, vitamins, nutritional supplements, and hormonal therapy are not recommended other than to correct specific deficiencies. (LoE: B) • In patients with HFrEF, class IC antiarrhythmic medication and dronedarone may increase risk of mortality. (LoE: A) • In patients with HFrEF, thiazolidinediones increase the risk of worsening HF symptoms and hospitalizations. (LoE: A) • In patients with type 2 diabetes and high cardiovascular risk, the DPP-4 inhibitors, saxagliptin and alogliptin, increase the risk of HF hospitalization and should be avoided in patients with HF. (LoE: B) • In patients with HFrEF, nonsteroidal anti-inflammatory drugs worsen HF symptoms and should be avoided or withdrawn whenever possible. (LoE: B) • For patients with symptomatic (NYHA class II to III) stable chronic HFrEF (LVEF ≤35%) who are receiving guideline-directed medical therapy, including a maximally tolerated dose of a beta blocker, and who are in sinus rhythm with a heart rate of ≥70 beats per minute at rest, ivabradine can be beneficial to reduce HF hospitalizations and cardiovascular death. (LoE: B) • In patients with symptomatic HFrEF despite guideline-directed medical therapy or who are unable to tolerate guideline-directed medical therapy, digoxin might be considered to decrease hospitalizations for HF. (LoE: B) • In select high-risk patients with HFrEF and recent worsening of HF already on guideline-directed medical therapy, an oral soluble guanylate cyclase stimulator (vericiguat) may be considered to reduce HF hospitalization and cardiovascular death. (LoE: B) <u>Pharmacological treatment for Stage C HF with mildly reduced EF and improved EF</u> • In patients with HF with mildly reduced EF, SGLT-2 inhibitors can be beneficial in decreasing HF hospitalizations and cardiovascular mortality. (LoE: B) • Among patients with current or previous symptomatic HF with mildly reduced EF (LVEF, 41 to 49%), use of evidence-based beta blockers for HFrEF, ARNI, ACE inhibitor or ARB, and mineralocorticoid receptor antagonists may be considered to reduce the risk of HF hospitalization and cardiovascular mortality, particularly among patients with LVEF on the lower end of this spectrum. (LoE: B) • In patients with HF with improved EF after treatment, guideline-directed medical therapy should be continued to prevent relapse of HF and LV dysfunction, even in patients who may become asymptomatic. (LoE: B) <u>Pharmacological treatment for Stage C HF with preserved EF (HFpEF)</u> • Patients with hypertension and HFpEF should have medication titrated to attain blood pressure targets in accordance with published clinical practice guidelines to prevent morbidity. (LoE: C) • SGLT-2 inhibitors can be beneficial in decreasing HF hospitalizations and cardiovascular mortality. (LoE: B) • In patients with HFpEF, the use of a mineralocorticoid receptor antagonist, ARB, or ARNI may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum. (LoE: B) • Routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or quality of life in patients with HFpEF is ineffective. (LoE: B) <u>Treatment of Stage D (advanced/refractory) HF</u> • For patients with advanced HF and hyponatremia, the benefit of fluid restriction to reduce congestive symptoms is uncertain. (LoE: C) • Continuous intravenous inotropic support is reasonable as “bridge therapy” in patients with HF (Stage D) refractory to guideline-directed medical therapy and

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	device therapy who are eligible for and awaiting mechanical circulatory support or cardiac transplantation. (LoE: B) • In select patients with HF Stage D, despite optimal guideline-directed medical therapy and device therapy who are ineligible for either mechanical circulatory support or cardiac transplantation, continuous intravenous inotropic support may be considered as palliative therapy for symptom control and improvement in functional status. (LoE: B) • Long-term use of either continuous or intermittent, intravenous inotropic agents, for reasons other than palliative care or as a bridge to advanced therapies, is potentially harmful. (LoE: B)
European Society of Cardiology: **Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (2021)**[30]	<u>Pharmacological treatments indicated in patients with (NYHA Class II-IV) heart failure with reduced ejection fraction</u> • An ACE inhibitor is recommended, in addition to a β-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death. • A mineralocorticoid receptor antagonist (MRA) is recommended for patients with HFrEF, who remain symptomatic despite treatment with an ACE inhibitor and a β-blocker, to reduce the risk of HF hospitalization and death. • Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death. Dapagliflozin or empagliflozin are recommended, in addition to optimal medical therapy with an ACE-I/ARNI, a β-blocker and an MRA, for patients with HFrEF regardless of diabetes status. • Sacubitril-valsartan is recommended as a replacement for an ACE inhibitor to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE inhibitor, a β-blocker, and a mineralocorticoid receptor antagonist. • Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion. • Ivabradine should be considered to reduce the risk of HF hospitalization or cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm despite treatment with an evidence-based dose of β-blocker (or maximum tolerated dose below that), ACE inhibitor (or ARB), and a mineralocorticoid receptor antagonist (or ARB). • Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm who are unable to tolerate or have contraindications for a β-blocker. Patients should also receive an ACE inhibitor (or ARB) and a mineralocorticoid receptor antagonist (or ARB). • An ARB is recommended to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients unable to tolerate an ACE inhibitor (patients should also receive a β-blocker and mineralocorticoid receptor antagonist). • An ARB may be considered to reduce the risk of HF hospitalization and death in patients who are symptomatic despite treatment with a β-blocker who are unable to tolerate a mineralocorticoid receptor antagonist. • Vericiguat may be considered in patients in NYHA class II-IV who have had worsening HF despite treatment with an ACE-I (or ARNI), a β-blocker and an MRA to reduce the risk of CV mortality or HF hospitalization. • Hydralazine and isosorbide dinitrate should be considered in self-identified black patients with LVEF ≤35% or with an LVEF <45% combined with a dilated LV in NYHA Class III–IV despite treatment with an ACE-I a β-blocker and a mineralocorticoid receptor antagonist to reduce the risk of HF hospitalization and death. • Hydralazine and isosorbide dinitrate may be considered in symptomatic patients with HFrEF who can tolerate neither an ACE inhibitor nor an ARB (or they are contraindicated) to reduce the risk of death.

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	• Digoxin is a treatment with less-certain benefits and may be considered in symptomatic patients in sinus rhythm despite treatment with an ACE inhibitor (or ARB), a β-blocker and a mineralocorticoid receptor antagonist, to reduce the risk of hospitalization (both all-cause and HF-hospitalizations). <u>Recommendations for treatment of patients with (NYHA class II-IV) heart failure with mildly reduced ejection fraction (HFmrEF)</u> • Diuretics are recommended in patients with congestion and HFmrEF in order to alleviate symptoms and signs. • An ACE inhibitor may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • An ARB may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • A β-blocker may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • An MRA may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • Sacubitril/valsartan may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. <u>Recommendations for treatment of patients with heart failure with preserved ejection fraction (HFpEF)</u> • It is recommended to screen patients with HFpEF for both cardiovascular and noncardiovascular comorbidities, which, if present, should be treated provided safe and effective interventions exist to improve symptoms, well-being and/or prognosis. • Diuretics are recommended in congested patients with HFpEF in order to alleviate symptoms and signs. <u>Recommendations for the primary prevention of heart failure in patients with risk factors for its development</u> • Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life. • Treatment with statins is recommended in patients at high risk of CV disease or with CV disease in order to prevent or delay the onset of HF, and to prevent HF hospitalizations. • SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with diabetes at high risk of CV disease or with CV disease in order to prevent HF hospitalizations. • Counselling against sedentary habit, obesity, cigarette smoking, and alcohol abuse is recommended to prevent or delay the onset of HF. <u>Recommendations for the initial management of patients with acute heart failure – pharmacotherapy</u> • Intravenous loop diuretics are recommended for all patients with acute HF admitted with signs/symptoms of fluid overload to improve symptoms. It is recommended to regularly monitor symptoms, urine output, renal function and electrolytes during use of intravenous diuretics. • Combination of a loop diuretic with thiazide type diuretic should be considered in patients with resistant oedema who do not respond to an increase in loop diuretic doses. • In patients with acute HF and SBP >110 mmHg, intravenous vasodilators may be considered as initial therapy to improve symptoms and reduce congestion. • Inotropic agents may be considered in patients with SBP <90 mmHg and evidence of hypoperfusion who do not respond to standard treatment, including

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	fluid challenge, to improve peripheral perfusion and maintain end-organ function. • Inotropic agents are not recommended routinely, due to safety concerns, unless the patient has symptomatic hypotension and evidence of hypoperfusion. • A vasopressor, preferably norepinephrine, may be considered in patients with cardiogenic shock to increase blood pressure and vital organ perfusion. • Thromboembolism prophylaxis (e.g. with LMWH) is recommended in patients not already anticoagulated and with no contraindication to anticoagulation, to reduce the risk of deep venous thrombosis and pulmonary embolism. • Routine use of opiates is not recommended, unless in selected patients with severe/intractable pain or anxiety.
Eighth Joint National Committee (JNC 8): **2014 Evidence-based Guideline for the Management of High Blood Pressure in Adults (2014)**[31]	• Pharmacologic treatment should be initiated in patients ≥60 years of age to lower blood pressure at systolic blood pressure ≥150 mm Hg or diastolic blood pressure ≥90 mm Hg and to a goal systolic blood pressure <150 mm Hg and goal diastolic blood pressure <90 mm Hg. Adjustment of treatment is not necessary if treatment results in lower blood pressure and treatment is well tolerated and without adverse effects on health or quality of life. • In patients <60 years of age, pharmacologic treatment should be initiated to lower blood pressure at diastolic blood pressure ≥90 mm Hg to a goal diastolic blood pressure <90 mm Hg. • In patients <60 years of age, pharmacologic treatment should be initiated to lower blood pressure at systolic blood pressure ≥150 mm Hg to a goal diastolic blood pressure <140 mm Hg. • For patients ≥18 years of age with chronic kidney disease or diabetes, pharmacologic treatment should be initiated to lower blood pressure at systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg and to a goal systolic blood pressure <140 mm Hg and goal diastolic blood pressure <90 mm Hg. • Initial antihypertensive treatment for the general nonblack population, including those with diabetes, should include thiazide-type diuretic, calcium channel blocker (CCB), ACE inhibitor, or ARB. • Initial antihypertensive treatment for the general black population, including those with diabetes, should include thiazide-type diuretic or CCB. • For patients ≥18 years of age with chronic kidney disease regardless of race or diabetes status, initial (or add-on) treatment should include an ACE inhibitor or ARB to improve kidney outcomes. • The main goal of antihypertensive treatment is to attain and maintain goal blood pressure. • If goal blood pressure is not attained within a month of treatment, the dose of the initial drug should be increased or second drug from the thiazide-type diuretic, CCB, ACE inhibitor, or ARB classes should be added. • If goal is not achieved with two drugs, a third drug from the thiazide-type diuretic, CCB, ACE inhibitor, or ARB classes should be added. • An ACE inhibitor and ARB should not be used together. • Antihypertensive classes can be used if the patient is unable to achieve goal blood pressure with three agents or had a contraindication to a preferred class. • If blood pressure is not able to be achieved or in complicated patients, referral to a hypertension specialist may be indicated.
International Society of Hypertension: **Global Hypertension Practice Guidelines (2020)**[32]	<u>Lifestyle modifications</u> • Lifestyle modification is the first line of antihypertensive treatment. • Salt reduction: Reduce salt added when preparing foods, and at the table. Avoid or limit consumption of high salt foods such as soy sauce, fast foods and processed food including breads and cereals high in salt. • Healthy diet: Eating a diet that is rich in whole grains, fruits, vegetables, polyunsaturated fats and dairy products and reducing food high in sugar, saturated fat and trans fats, such as the DASH diet.

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	• Healthy drinks: Moderate consumption of coffee, green and black tea. Other beverages that can be beneficial include karkadé (hibiscus) tea, pomegranate juice, beetroot juice and cocoa. • Moderation of alcohol consumption: The recommended daily limit for alcohol consumptions is 2 standard drinks for men and 1.5 for women (10 g alcohol/standard drink). Avoid binge drinking. • Weight reduction: Body weight control is indicated to avoid obesity. Particularly abdominal obesity should be managed. Ethnic-specific cut-offs for BMI and waist circumference should be used. Alternatively, a waist-to-height ratio <0.5 is recommended for all populations. • Smoking cessation: Smoking is a major risk factor for cardiovascular disease (CVD), COPD and cancer. Smoking cessation and referral to smoking cessation programs are advised. • Regular physical activity: Studies suggest that regular aerobic and resistance exercise may be beneficial for both the prevention and treatment of hypertension. Moderate intensity aerobic exercise (walking, jogging, cycling, yoga, or swimming) for 30 minutes on five to seven days per week Strength training also can help reduce blood pressure. Performance of resistance/strength exercises on two to three days per week. • Reduce stress and induce mindfulness: Stress should be reduced and mindfulness or meditation introduced into the daily routine. • Reduce exposure to air pollution and cold temperature: Evidence from studies support a negative effect of air pollution on blood pressure in the long-term. <u>Pharmacological Treatment</u> • Ideal characteristics of drug treatment o Treatments should be evidence-based in relation to morbidity/mortality prevention. o Use a once-daily regimen which provides 24-hour blood pressure control. o Treatment should be affordable and/or cost-effective relative to other agents. o Treatments should be well-tolerated. o Evidence of benefits of use of the medication in populations to which it is to be applied. • General scheme for drug treatment o Lifestyle modification is the first line of antihypertensive treatment. o Grade 1 hypertension (BP 140 to 159/ 90 to 99): Immediate drug treatment in high-risk patients or those with CVD, chronic kidney disease (CKD), diabetes mellitus (DM), or hypertension-mediated organ damage (HMOD). Drug treatment after three to six months of lifestyle intervention if BP still not controlled in low to moderate risk patients. o Grade 2 hypertension (BP ≥160/100): Immediate drug treatment in all patients. • Core drug-treatment strategy o Step 1: Dual low-dose combination (ACE inhibitor or ARB plus dihydropyridine-calcium channel blockers (DHP-CCB)); consider monotherapy in low-risk grade 1 hypertension or in very old (≥80 years) or frail patients; consider ACE/ARB plus thiazide-like diuretic in post-stroke, very elderly, incipient HF, or CCB intolerance; consider ACE/ARB plus DHP-CCB or DHP-CCB plus thiazide-like diuretics in black patients. o Step 2: Dual full-dose combination (ACE inhibitor or ARB plus DHP-CCB); consider monotherapy in low-risk grade 1 hypertension or in very old (≥80 years) or frail patients; consider ACE/ARB plus thiazide-like diuretic in post-stroke, very elderly, incipient HF, or CCB intolerance.

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	○ Step 3: Triple combination (ACE/ARB plus DHP-CCB plus thiazide-like diuretic). ○ Step 4, resistant hypertension: triple combination plus spironolactone or other drug, alternatives include amiloride, doxazosin, eplerenone, clonidine, or β-blocker. Caution with spironolactone or other potassium sparing diuretics when estimated GFR <45 mL/min/1.73m^2 or K+ >4.5 mmol/L. ○ Consider β-blockers at any treatment step when there is a specific indications for their use, e.g., heart failure, angina, post-MI, atrial fibrillation, or younger women planning pregnancy or pregnant.
Hypertension Canada: **2020 Guidelines for the Prevention, Diagnosis, Risk Assessment, and Treatment of Hypertension in Adults and Children (2020)**[33]	<u>Indications for drug therapy for adults with hypertension without compelling indications for specific agents</u> • Antihypertensive therapy should be prescribed for average diastolic blood pressure (DBP) measurements of ≥100 mmHg or average systolic blood pressure (SBP) measurements of ≥160 mmHg in patients without macrovascular target organ damage or other cardiovascular risk factors. • Antihypertensive therapy should be strongly considered for average DPB readings ≥90 mmHg or for average SBP readings ≥140 mmHg in the presence of macrovascular target organ damage or other independent cardiovascular risk factors. • For high-risk patients, aged 50 years or older, with SBP levels ≥130 mmHg, intensive management to target a SBP <120 mmHg should be considered. Patient selection for intensive management is recommended and caution should be taken in certain high-risk groups. <u>Indications for drug therapy for adults with diastolic and with or without systolic hypertension</u> • Initial therapy should be with either monotherapy or single pill combination (SPC). ○ Recommended monotherapy choices are: ▪ A thiazide/thiazide-like diuretic, with longer-acting diuretics preferred; ▪ A β-blocker (in patients <60 years of age); ▪ An angiotensin-converting enzyme (ACE) inhibitor (in nonblack patients); ▪ An angiotensin receptor blocker (ARB); or ▪ A long-acting calcium channel blocker (CCB). ○ Recommended SPC choices are those in which an ACE inhibitor is combined with a CCB, ARB with a CCB, or ACE inhibitor or ARB with a diuretic. ○ Hypokalemia should be avoided in patients treated with thiazide/thiazide-like diuretic monotherapy. • Additional antihypertensive drugs should be used if target BP levels are not achieved with standard-dose monotherapy. Add-on drugs should be chosen from first-line choices. Useful choices include a thiazide/thiazide-like diuretic or CCB with either: ACE inhibitor, ARB, or β-blocker. Caution should be exercised in combining a nondihydropyridine CCB and a β-blocker. The combination of an ACE inhibitor and an ARB is not recommended. • If BP is still not controlled with a combination of two or more first-line agents, or there are adverse effects, other antihypertensive drugs may be added. • Possible reasons for poor response to therapy should be considered. • α-Blockers are not recommended as first-line agents for uncomplicated hypertension; β-blockers are not recommended as first-line therapy for uncomplicated hypertension in patients ≥60 years of age; and ACE inhibitors are not recommended as first-line therapy for uncomplicated hypertension in black patients. However, these agents may be used in patients with certain comorbid

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	conditions or in combination therapy. Indications for drug therapy for adults with isolated systolic hypertension • Initial therapy should be single-agent therapy with a thiazide/thiazide-like diuretic, a long-acting dihydropyridine CCB, or an ARB. If there are adverse effects, another drug from this group should be substituted. Hypokalemia should be avoided in patients treated with thiazide/thiazide-like diuretic monotherapy. • Additional antihypertensive drugs should be used if target BP levels are not achieved with standard-dose monotherapy. Add-on drugs should be chosen from first-line options. • If BP is still not controlled with a combination of two or more first-line agents, or there are adverse effects, other classes of drugs (such as α-blockers, ACE inhibitors, centrally acting agents, or nondihydropyridine CCBs) may be combined or substituted. • Possible reasons for poor response to therapy should be considered. • α-Blockers are not recommended as first-line agents for uncomplicated isolated systolic hypertension; and β-blockers are not recommended as first-line therapy for isolated systolic hypertension in patients ≥60 years of age. However, both agents may be used in patients with certain comorbid conditions or in combination therapy. Guidelines for hypertensive patients with coronary artery disease (CAD) • For most hypertensive patients with CAD, an ACE inhibitor or ARB is recommended. • For hypertensive patients with CAD, but without coexisting systolic heart failure, the combination of an ACE inhibitor and ARB is not recommended. • For high-risk hypertensive patients, when combination therapy is being used, choices should be individualized. The combination of an ACE inhibitor and a dihydropyridine CCB is preferable to an ACE inhibitor and a thiazide/thiazide-like diuretic in selected patients. • For patients with stable angina pectoris but without previous heart failure, myocardial infarction, or coronary artery bypass surgery, either a β-blocker or CCB can be used as initial therapy. • Short-acting nifedipine should not be used. • When decreasing SBP to target levels in patients with established CAD (especially if isolated systolic hypertension is present), be cautious when the DBP is ≤60 mmHg because of concerns that myocardial ischemia might be exacerbated, especially in patients with left ventricular hypertrophy (LVH). Guidelines for patients with hypertension who have had a recent myocardial infarction • Initial therapy should include a β-blocker as well as an ACE inhibitor. • An ARB can be used if the patient is intolerant of an ACE inhibitor. • CCBs may be used in patients after myocardial infarction when β-blockers are contraindicated or not effective. Nondihydropyridine CCBs should not be used when there is heart failure, evidenced by pulmonary congestion on examination or radiography. Treatment of hypertension in association with heart failure • In patients with systolic dysfunction (ejection fraction <40%), ACE inhibitors and β-blockers are recommended for initial therapy. Aldosterone antagonists (mineralocorticoid receptor antagonists) may be combined in treatment for patients with a recent cardiovascular hospitalization, acute myocardial infarction, elevated B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide level, or New York Heart Association (NYHA) Class II-IV symptoms. Careful

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	monitoring for hyperkalemia is recommended when combining an aldosterone antagonist with ACE inhibitor or ARB treatment. Other diuretics are recommended as additional therapy if needed. Beyond considerations of BP control, doses of ACE inhibitors or ARBs should be titrated to those reported to be effective in trials unless adverse effects become manifest.
	• An ARB is recommended if ACE inhibitors are not tolerated.
	• A combination of hydralazine and isosorbide dinitrate is recommended if ACE inhibitors and ARBs are contraindicated or not tolerated.
	• For hypertensive patients whose BP is not controlled, an ARB may be combined with an ACE inhibitor and other antihypertensive drug treatment. Careful monitoring should be used if combining an ACE inhibitor and an ARB because of potential adverse effects such as hypotension, hyperkalemia, and worsening renal function. Additional therapies may also include dihydropyridine CCBs.
	• An angiotensin receptor-neprilysin inhibitor (ARNI) should be used in place of an ACE inhibitor or ARB for patients with HFrEF (<40%) who remain symptomatic despite treatment with appropriate dose of guideline directed HF therapy. Eligible patients must have a serum potassium <5.2 mmol/L, an eGFR ≤30 mL/min/1.73m^2 and close surveillance of serum potassium and creatinine.
	
	<u>Treatment of hypertension in association with stroke</u>
	• BP management in acute ischemic stroke (onset to 72 hours)
	  o Please refer to Stroke Best Practice recommendations.
	• BP management after acute ischemic stroke
	  o Strong consideration should be given to the initiation of antihypertensive therapy after the acute phase of a stroke or transient ischemic attack.
	  o After the acute phase of a stroke, BP-lowering treatment is recommended to a target of consistently <140/90 mmHg.
	  o Treatment with an ACE inhibitor and thiazide/thiazide-like diuretic combination is preferred.
	  o For patients with stroke, the combination of an ACE inhibitor and ARB is not recommended.
	• BP management in hemorrhagic stroke (onset to 72 hours)
	  o Please refer to Stroke Best Practice recommendations.
	
	<u>Treatment of hypertension in association with LVH</u>
	• Hypertensive patients with LVH should be treated with antihypertensive therapy to decrease the rate of subsequent cardiovascular events.
	• The choice of initial therapy can be influenced by the presence of LVH. Initial therapy can be drug treatment using ACE inhibitors, ARBs, long-acting CCBs, or thiazide/thiazide-like diuretics. Direct arterial vasodilators such as hydralazine or minoxidil should not be used.
	
	<u>Treatment of hypertension in association with nondiabetic chronic kidney disease</u>
	• Individualize BP targets in patients with chronic kidney disease. Consider intensive targets (SBP <120 mmHg) in appropriate patients.
	• For patients with hypertension and proteinuric chronic kidney disease (urinary protein >150 mg per 24 hours or albumin to creatinine ratio >30 mg/mmol), initial therapy should be an ACE inhibitor or an ARB if there is intolerance to ACE inhibitors.
	• In most cases, combination therapy with other antihypertensive agents might be needed to reach target BP levels.
	• The combination of an ACE inhibitor and ARB is not recommended for patients with nonproteinuric chronic kidney disease.
	
	<u>Treatment of hypertension in association with renovascular disease</u>

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	• Patients with hypertension attributable to atherosclerotic renal artery stenosis should be primarily medically managed because renal angioplasty and stenting offers no benefit over optimal medical therapy alone. • Renal artery angioplasty and stenting for atherosclerotic hemodynamically significant renal artery stenosis could be considered for patients with uncontrolled hypertension resistant to maximally tolerated pharmacotherapy, progressive renal function loss, and acute pulmonary edema. • Patients with confirmed renal fibromuscular dysplasia (FMD) should be referred to a hypertension specialist. • Renal artery angioplasty without stenting is recommended for treatment of FMD-related renal artery stenosis. Stenting is not recommended unless needed because of a periprocedural dissection. Surgical revascularization should be considered in cases of complex lesions less amendable to angioplasty, stenosis associated with complex aneurysm, and restenosis despite two unsuccessful attempts of angioplasty. <u>Treatment of hypertension in association with diabetes mellitus</u> • Persons with diabetes mellitus should be treated to attain SBP of <130 mmHg and DBP of <80 mmHg. • For persons with cardiovascular or kidney disease, including microalbuminuria, or with cardiovascular risk factors in addition to diabetes and hypertension, an ACE inhibitor or an ARB is recommended as initial therapy. • For persons with diabetes and hypertension not included in other guidelines in this section, appropriate choices include (in alphabetical order): ACE inhibitors, ARBs, dihydropyridine CCBs, and thiazide/thiazide-like diuretics. • If target BP levels are not achieved with standard-dose monotherapy, additional antihypertensive therapy should be used. For persons in whom combination therapy with an ACE inhibitor is being considered, a dihydropyridine CCB is preferable to a thiazide/thiazide-like diuretic. <u>Resistant hypertension</u> • Resistant hypertension is defined as BP above target despite three or more BP-lowering drugs at optimal doses preferably including a diuretic (and usually a renin-angiotensin-aldosterone system blocker and a CCB. • Accurate office and out-of-office BP measurement is essential. • Other reasons for apparent resistant hypertension should be eliminated before diagnosing true resistant hypertension, including nonadherence, white coat effect, and secondary hypertension. • Pharmacotherapy with the additional use of spironolactone, bisoprolol, doxazosin, amiloride, eplerenone, or clonidine with the baseline regimen decreases BP significantly, with the greatest BP-lowering shown with spironolactone. • Patients with resistant hypertension should be referred to providers with expertise in diagnosis and management of hypertension. <u>Hypertension and pediatrics</u> • BP should be measured regularly in children three years of age or older; the auscultatory method is the gold-standard at present. • Initial therapy should be monotherapy, with an ACE inhibitor or ARB (not first-line in black children), or a long-acting dihydropyridine CCB. • The treatment t goal is systolic and diastolic office BP and/or ABPM < 95th percentile or <90th percentile in children with risk factors or target organ damage. • Complex cases should be referred to an expert in pediatric hypertension. <u>Hypertension and pregnancy</u>

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	• Up to 7% of pregnancies are complicated by a hypertensive disorder of pregnancy, and approximately 5% of women will have chronic hypertension when they become pregnant. • The prevalence of hypertension in pregnancy is expected to increase with women becoming pregnant later in their reproductive years and the increasing prevalence of cardiovascular comorbidities such as increased preconception body mass index and maternal diabetes. • The possibility of pregnancy should be considered when managing women with hypertension who are of reproductive age. • Preconception counselling should be offered to all women with hypertension who are considering pregnancy. • ACE inhibitor and ARB therapy should be avoided before conception and during pregnancy unless there is a compelling indication for their use (i.e., proteinuric kidney disease). • Hypertension during pregnancy can increase the risk of adverse maternal and fetal outcomes, including an increased risk of preeclampsia, placental abruption, prematurity, small for gestational age infants, stillbirth, and maternal renal and retinal injury, thus generally requires involvement of an interdisciplinary team including obstetrical care providers. • Antihypertensive therapy is recommended for average SBP measurements of ≥140 mmHg or DBP measurements of ≥90 mmHg in pregnant women with chronic hypertension, gestational hypertension, or preeclampsia. Initial antihypertensive therapy should be monotherapy from the following first-line drugs: oral labetalol, oral methyldopa, long-acting oral nifedipine, or other oral b-blockers (acebutolol, metoprolol, pindolol, and propranolol). Other antihypertensive drugs can be considered as second-line drugs including: clonidine, hydralazine, and thiazide diuretics. • Women with severe hypertension with SBP ≥160 mmHg or DBP ≥110 mmHg in pregnancy or postpartum require urgent antihypertensive therapy because it is considered an obstetrical emergency. • Antihypertensive drugs used in breastfeeding women include: labetalol, methyldopa, long-acting nifedipine, enalapril, or captopril.
European Society of Hypertension: **2023 Guidelines for the management of arterial hypertension (2023)**[34]	General recommendations for antihypertensive drug treatment • BP lowering should be prioritized over the selection of specific antihypertensive drug classes because treatment benefit largely originates from BP reduction. • Five major drug classes including, ACE inhibitors, ARBs, β-blockers, CCBs, and Thiazide/Thiazide-like diuretics have effectively reduced blood pressure and cardiovascular events in randomized controlled trials. These drugs and their combinations are recommended as the basis of antihypertensive treatment strategies. • Initiation of therapy with a two-drug combination is recommended for most hypertensive patients. Preferred combinations should comprise a RAS blocker (either an ACE inhibitor or an ARB) with a CCB or thiazide/thiazide-like diuretic. Other combinations of the five major drug classes can be used. • Initiation with monotherapy can be considered in patients with: grade 1 hypertension and low-risk if BP is only marginally elevated (less than 150 mmHg SBP and 95 mmHg DBP) high-normal BP and very high cardiovascular risk, frailty and/or and advance age. • If BP is not controlled with the initial two-drug combination by using the maximum recommended and tolerated dose of the respective components, treatment should be increased to a three-drug combination, usually a RAS blocker plus CCB plus thiazide/thiazide-like diuretic. • If BP is not controlled with a three-drug combination by using the maximum recommended and tolerated dose of the respective components, it is recommended to extend treatment according to the recommendations for resistant

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	hypertension. • The use of single pill combinations should be preferred at any treatment step (i.e. during initiation of therapy with a two-drug combination and at any other step of treatment). • β-blocker should be used at initiation of therapy or at any treatment step as guideline-directed medical therapy (e.g., heart failure with reduced ejection fraction, anti-ischemic therapy in chronic coronary syndromes, heart rate control in atrial fibrillation). • β-blockers can be considered in the presence of several other conditions in which their use can be favorable. • The combination of two RAS blockers is not recommended due to increased risk of adverse events, in particular AKI. True-resistant hypertension • In resistant hypertension, it is recommended to reinforce lifestyle measures. • Drugs that can be considered as additional therapy in patients with resistant hypertension are preferably spironolactone (or other MRA), or β-blocker or Alpha-1 blockers or centrally acting agents (clonidine), or amiloride. • Thiazide/thiazide-like diuretics are recommended in resistant hypertension if estimated eGFR is ≥30 mL/min/1.73m^2. • Loop diuretics may be considered in patients with an estimated eGFR < 45 mL/min/1.73m^2 and should be used if eGFR falls below 30 mL/min/1.73m^2. • Chlorthalidone (12.5 to 25 mg once daily) could be used with or without a loop diuretic if eGFR is <30 mL/min/1.73m^2. • Renal deprivation can be considered as an additional treatment option in patients with resistant hypertension if eGFR is >40 mL/min/1.73m^2. • Patients with resistant hypertension should be followed very closely. Follow-up includes periodical ambulatory blood pressure monitoring and assessment of hypertension-mediated organ damage, particularly kidney function and serum potassium levels. Regular use of home blood pressure monitoring and monitoring of drug adherence are desirable.
National Institute for Health and Clinical Excellence: **Hypertension in adults: diagnosis and management (2019)**[35]	Choosing antihypertensive drug treatment (for people with or without type II diabetes) • Where possible, recommend treatment with drugs taken only once a day. • Prescribe non-proprietary drugs where these are appropriate and minimize cost. • Offer people with isolated systolic hypertension (systolic blood pressure ≥160 mmHg) the same treatment as people with both raised systolic and diastolic blood pressure. • Offer antihypertensive drug treatment to women of child-bearing potential with diagnosed hypertension in line with recommendations in this guideline. For women considering pregnancy or who are pregnant or breastfeeding, manage hypertension in line with the recommendations on Management of pregnancy with chronic hypertension and Breastfeeding in 'Hypertension in pregnancy'. • When choosing antihypertensive drug treatment for adults of black African or African-Caribbean family origin, consider an angiotensin II receptor blocker, in preference to an angiotensin-converting enzyme inhibitor. Step one treatment • Patients <55 years of age should be offered a step one antihypertensive with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). • Offer an ACE inhibitor or an ARB to adults starting step 1 antihypertensive treatment who have type II diabetes and are of any age or family origin or those aged <55 years but not of black African or African-Caribbean family origin.

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	• If an ACE inhibitor is not tolerated, offer an ARB. • Do not combine an ACE inhibitor with an ARB for the treatment of hypertension. • Offer a calcium channel blocker (CCB) to adults starting step 1 antihypertensive treatment who are >55 years of age and do not have diabetes and are of black African or African-Caribbean family origin and do not have type II diabetes and of any age. • If a CCB is not suitable, for example because of edema or intolerance, or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic. • If diuretic treatment is to be initiated or changed, offer a thiazide‑like diuretic, such as indapamide in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide. • For adults with hypertension who are already receiving treatment with bendroflumethiazide or hydrochlorothiazide, who have stable, well-controlled blood pressure, continue with their treatment. <u>Step two treatment</u> • Before considering next step treatment for hypertension discuss with the person if they are taking their medicine as prescribed and support adherence in line with NICE's guideline on "Medicines adherence: involving patients decisions about prescribed medicines and supporting adherence". • If hypertension is not controlled with a step one treatment of an ACE inhibitor or ARB, offer choice of one of the following drugs in addition to the step one treatment: a CCB or a thiazide-like diuretic. • If hypertension is not controlled in adults taking step one treatment of a CCB, offer the choice of one of the following drugs in addition to the step one treatment: an ACE inhibitor or an ARB or a thiazide-like diuretic. • If hypertension is not controlled in adults of black African or African–Caribbean family origin who do not have type 2 diabetes taking step one treatment, consider an ARB, in preference to an ACE inhibitor, in addition to step one treatment. <u>Step three treatment</u> • Before considering step three treatment, review the person's medications to ensure they are being taken at the optimal doses and discuss adherence (see recommendation under step two). • If hypertension is not controlled in adults taking step two treatment, offer a combination of an ACE inhibitor or ARB and a CCB and a thiazide-like diuretic. <u>Step four treatment</u> • If hypertension is not controlled in adults taking the optimal tolerated doses of an ACE inhibitor or an ARB plus a CCB and a thiazide-like diuretic, regard them as having resistant hypertension. • Before considering further treatment for a person with resistant hypertension, confirm elevated clinic blood pressure measurements using ambulatory or home blood pressure recordings, assess for postural hypotension, and discuss adherence. • For people with confirmed resistant hypertension, consider adding a fourth antihypertensive drug as step four treatment or seeking specialist advice. • Consider further diuretic therapy with low-dose spironolactone for adults with resistant hypertension starting step four treatment who have a blood potassium level of 4.5 mmol/l or less. Use particular caution in people with a reduced estimated glomerular filtration rate because they have an increased risk of hyperkalemia. • When using further diuretic therapy for step four treatment of resistant

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	hypertension, monitor blood sodium and potassium and renal function within one month of starting treatment and repeat as needed thereafter. • Consider an alpha-blocker or beta-blocker for adults with resistant hypertension starting step four treatment who have a blood potassium level of more than 4.5 mmol/l. • If blood pressure remains uncontrolled in people with resistant hypertension taking the optimal tolerated doses of four drugs, seek specialist advice.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in Blacks (2010)**[36]	• To attain and maintain blood pressure (BP) below target levels, multiple antihypertensive drugs will be required in most hypertensive blacks. • Use of two-drug combination therapy when SBP is >15 mm Hg and/or DBP is >10 mm Hg above goal levels is increasingly recommended as first-line therapy. • Two-drug regimens have generally contained a thiazide-type diuretic; however, the combination of a calcium channel blocker (CCB) with either an ACE inhibitor or an ARB has been shown equally efficacious in BP lowering but with demonstrated superiority (CCB+ACE) for hard clinical outcomes compared with the same ACE inhibitor plus a thiazide-type diuretic. • In secondary prevention patients, the combination therapy should include a drug(s) with the appropriate compelling indications. • Certain classes of antihypertensive medications, specifically diuretics and CCBs, lower BP on average more than β-blockers and renin-angiotensin system (RAS) blockers in black patients when used as monotherapies. • In the absence of compelling indications, when BP is near goal levels, monotherapy with a diuretic or a CCB is preferred. • Lifestyle modifications should be initiated in all patients with hypertension, whether or not pharmacotherapy is planned. • ACE inhibitors or ARBs are recommended as alternative monotherapy options in the treatment of hypertension in blacks. The rationale for their lower tier monotherapy recommendation is because they have consistently achieved lesser average reductions in BP relative to that observed with monotherapy using either a diuretic or CCB.
Kidney Disease Improving Clinical Outcomes Group: **KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease (2021)**[37]	<u>Blood pressure measurement</u> • The Work Group recommends standardized office blood pressure (BP) measurement in preference to routine office BP measurements for the management of high BP in adults. • The Work Group suggests that out-of-office BP measurements with ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM) be used to complement standardized office BP readings for the management of high BP. <u>Lifestyle interventions for lowering BP in patients with chronic kidney disease (CKD) not receiving dialysis</u> • The Work Group suggests targeting a sodium intake <2 grams of sodium per day (or <90 mmol of sodium per day, or <5 grams of sodium chloride per day) in patients with high BP and CKD. • The Work Group suggests that patients with high BP and CKD be advised to undertake moderate-intensity physical activity for a cumulative duration of at least 150 minutes per week, or to a level compatible with their cardiovascular and physical tolerance. <u>BP management in patients with CKD, with or without diabetes, not receiving dialysis</u> • The Work Group suggests that adults with high BP and CKD be treated with a target systolic BP (SBP) of <120 mmHg, when tolerated, using standardized office BP measurement. • The Work Group recommends starting renin-angiotensin-system inhibitors

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	(RASi) (angiotensin-converting enzyme inhibitor [ACEi] or angiotensin II receptor blocker [ARB]) for people with high BP, CKD, and severely increased albuminuria without diabetes. • The Work Group suggests starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately increased albuminuria without diabetes. • The Work Group recommends starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately-to-severely increased albuminuria with diabetes. • The Work Group recommends avoiding any combination of ACEi, ARB, and direct renin inhibitor (DRI) therapy in patients with CKD, with or without diabetes. <u>BP management in kidney transplant recipients</u> • Treat adult kidney transplant recipients with high BP to a target BP of <130 mmHg systolic and <80 mmHg diastolic using standardized office BP measurement. • The Work Group recommends that a dihydropyridine calcium channel blocker (CCB) or an ARB be used as the first-line antihypertensive agent in adult kidney transplant recipients. <u>BP management in children with CKD</u> • The Work Group suggests that in children with CKD, 24-hour mean arterial pressure by ABPM should be lowered to <50^{th} percentile for age, sex, and height.
American College of Cardiology/ American Heart Association Task Force: **Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults (2017)**[38]	<u>Initiation of Blood Pressure (BP) Treatment for Overall Cardiovascular Disease (CVD) Risk</u> • Use of BP-lowering medications is recommended for secondary prevention of recurrent CVD events in patients with clinical CVD and an average systolic blood pressure (SBP) ≥130 mmHg or an average diastolic blood pressure (DBP) of ≥80 mmHg and for primary prevention in adults with an estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk of ≥10% and an average SBP of ≥130 mmHg or an average ≥80 mmHg. • Use of BP-lowering medication is recommended for primary prevention of CVD in adults with no history of CVD and with an estimated 10-year ASCVD risk <10% and an SBP of ≥140 mmHg or a DBP of ≥90 mmHg. • Simultaneous use of an angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), and/or renin inhibitor is potentially harmful and is not recommended to treat adults with hypertension. • For adults with confirmed hypertension and known CVD or 10-year ASCVD risk of ≥10%, a BP target <130/80 mmHg is recommended. For adults with confirmed hypertension without additional markers of increased CVD risk, a BP target <130/80 mmHg may be reasonable. • For initiation of antihypertensive drug therapy, first-line agents include thiazide diuretics, calcium channel blockers (CCBs), and ACE inhibitors or ARBs. • Initiation of antihypertensive drug therapy with two first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended in adults with stage 2 hypertension and an average BP >20/10 mmHg above their BP target. • Initiation of antihypertensive drug therapy with a single antihypertensive drug is reasonable in adults with stage 1 hypertension and BP goal <130/80 mmHg with dosage titration and sequential addition of other agents to achieve the BP target. <u>Stable Ischemic Heart Disease (SIHD)</u> • In adults with SIHD and hypertension, a BP target <130/80 is recommended. • Adults with SIHD and hypertension (BP <u>≥</u>130/80 mmHg) should be treated with medications [e.g., guideline-directed medical therapy (GDMT) beta-blockers, ACE inhibitors, or ARBs] for compelling indications [e.g., previous myocardial

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	infarction (MI), stable angina] as first-line therapy, with the addition of other drugs (e.g., dihydropyridine CCBs, thiazide diuretics, and/or mineralocorticoid receptor antagonists) as needed to further control hypertension. • In adults with SIHD with angina and persistent uncontrolled hypertension, the addition of dihydropyridine CCBs to GDMT beta-blockers is recommended. • In adults who have had a MI or acute coronary syndrome, it is reasonable to continue GDMT beta-blockers beyond three years as long-term therapy for hypertension. • Beta-blockers and/or CCBs might be considered to control hypertension in patients with coronary artery disease (CAD) had an MI more than three years ago and have angina. Heart Failure • In adults with increased risk of HF, the optimal BP in those with hypertension should be <130 mmHg. • Adults with HFrEF and hypertension should be prescribed GDMT titrated to attain a BP <130/80 mmHg. • Non-dihydropyridine CCBs are not recommended in the treatment of hypertension in adults with HFrEF. • In adults with HFpEF who present with symptoms of volume overload, diuretics should be prescribed to control hypertension. • Adults with HFpEF and persistent hypertension after management of volume overload should be prescribed ACE inhibitors or ARBs and beta-blockers titrated to attain SBP <130 mmHg. CKD • Adults with hypertension and CKD should be treated to a BP goal <130/80 mmHg. • In adults with hypertension and CKD [stage 3 or higher or stage 1 or 2 with albuminuria (≥300 mg/d, or ≥300 mg/g albumin-to-creatinine ratio or the equivalent in the first morning void)], treatment with an ACE inhibitor is reasonable to slow kidney disease progression. Treatment with an ARB may be reasonable if an ACE inhibitor is not tolerated. • After kidney transplantation, it is reasonable to treat patients with hypertension to a BP goal <130/80 mmHg and with a CCB on the basis of improved glomerular filtration rate (GFR) and kidney survival. Cerebrovascular Disease • In adults with intracerebral hemorrhage (ICH) who present with SBP >220 mmHg, it is reasonable to use continuous intravenous (IV) drug infusion and close BP monitoring to lower levels. Immediate lowering of SBP to <140 mmHg in adults with spontaneous ICH who present within six hours of the acute event and have an SBP between 150 mmHg and 220 mmHg is not of benefit to reduce death or severe disability and can be potentially harmful. • Adults with acute ischemic stroke and elevated BP who are eligible for treatment with IV tissue plasminogen activator (tPA) should have their BP slowly lowered to <185/110 mmHg before thrombolytic therapy is initiated. • In adults with an acute ischemic stroke, BP should be <185/110 mmHg before administration of IV tPA and should be maintained below 180/105 mmHg for at least the first 24 hours after initiation drug therapy. • Starting or restarting antihypertensive therapy during hospitalization in patients with BP >140/90 mmHg who are neurologically stable is safe and reasonable to improve long-term BP control, unless contraindicated. • In patient with BP ≥220/120 mmHg who did not receive IV alteplase or endovascular treatment and have no comorbid conditions requiring acute

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	antihypertensive treatment, the benefit of initiating or reinitiating treatment of hypertension within the first 48 to 72 hours is uncertain. It might be reasonable to lower BP by 15% during the first 24 hours after onset of stroke. In patients with BP <220/120 mmHg with the same conditions, initiating or reinitiating treatment of hypertension within the first 48 to 72 hours after an acute ischemic stroke is not effective to prevent death or dependency. • Adults with previously treated stroke or transient ischemic attack should be restarted on antihypertensive treatment after the first few days of the index event to reduce the risk of recurrent stroke and other vascular events. Treatment with a thiazide diuretic, ACE inhibitor, or ARB, or combination treatment consisting of a thiazide diuretic plus ACE inhibitor, is useful. • Adults not previously treated for hypertension who experienced a stroke or transient ischemic attack and have an established BP ≥140/90 mmHg should be prescribed antihypertensive treatment a few days after the index event to reduce the risk of recurrent stroke and other vascular event. • For adults who experience a stroke or transient ischemic attack, selection of specific drugs should be individualized on the basis of patient comorbidities and agent pharmacological class. • For adults who experience a stroke or transient ischemic attack, a BP goal <130/80 mmHg may be reasonable. • For adults with a lacunar stroke, a target SBP goal <130 mmHg may be reasonable. • In adults previously untreated for hypertension who experience an ischemic stroke or transient ischemic attack and have an SBP <140 mmHg and a DBP <90 mmHg, the usefulness of initiating antihypertensive treatment is not well established. <u>Peripheral Artery Disease (PAD)</u> • Adults with hypertension and PAD should be treated similarly to patients with hypertension without PAD. <u>Diabetes Mellitus (DM)</u> • In adults with DM and hypertension, antihypertensive drug treatment should be initiated at a BP of ≥130/80 mmHg with a treatment goal <130/80 mmHg. • In adults with DM and hypertension, all first-line classes of antihypertensive agents (i.e., diuretics, ACE inhibitors, ARBs, and CCBs) are useful and effective. • In adults with DM and hypertension, ACE inhibitors or ARBs may be considered in the presence of albuminuria. <u>Atrial Fibrillation, Valvular Heart Disease, and Aortic disease</u> • Treatment of hypertension can be useful for prevention of recurrence of AF. • In adults with asymptomatic aortic stenosis, hypertension should be treated with pharmacotherapy, starting at a low dose and gradually titrating upward as needed. • In patients with chronic aortic insufficiency, treatment of systolic hypertension with agents that do not slow the heart rate (i.e., avoid beta-blockers) is reasonable. • Beta-blockers are recommended as the preferred antihypertensive agents in patients with hypertension and thoracic aortic disease. <u>Racial and Ethnic Differences in Treatment</u> • In black adults with hypertension but without HF or CKD, including those with DM, initial antihypertensive treatment should include a thiazide-type diuretic or CCB. Two or more antihypertensive medications are recommended to achieve a BP target <130/80 mmHg in most adults with hypertension, especially in black adults with hypertension.

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	Pregnancy • Women with hypertension who become pregnant, or are planning to become pregnant, should be transitioned to methyldopa, nifedipine, and/or labetalol during pregnancy. • Women with hypertension who become pregnant should not be treated with ACE inhibitors, ARBs, or direct renin inhibitors. Older Persons • Treatment of hypertension with an SBP treatment goal <130 mmHg is recommended for noninstitutionalized ambulatory community-dwelling adults (≥65 years of age) with an average SBP of ≥130 mmHg. • For older adults (≥65 years of age) with hypertension and a higher burden of comorbidity and limited life expectancy, clinical judgment, patient preference, and a team-based approach to assess risk/benefit is reasonable for decisions regarding intensity of BP lowering and choice of antihypertensive drugs. Hypertensive Crises • In adults with a hypertensive emergency, admission to an intensive care unit is recommended for continuous monitoring of BP and target organ damage and for parenteral administration of an appropriate agent. • For adults with a compelling condition (i.e., aortic dissection, severe pre-eclampsia or eclampsia, or pheochromocytoma crisis), SBP should be reduced to <140 mmHg during the first hour and to <120 mmHg in aortic dissection. • For adults without a compelling condition, SBP should be reduced by no more than 25% within the first hours; then, if stable, to 160/100 mmHg within the next two to six hours; and then cautiously to normal during the following 24 to 48 hours. Cognitive Decline and Dementia • In adults with hypertension, BP lowering is reasonable to prevent cognitive decline and dementia. Patients Undergoing Surgical Procedures • In patients with hypertension undergoing major surgery who have been on beta-blockers chronically, beta-blockers should be continued. • In patients with hypertension undergoing planned elective major surgery, it is reasonable to continue medical therapy for hypertension until surgery. • In patients with hypertension undergoing major surgery, discontinuation of ACE inhibitors or ARBs perioperatively may be considered. • In patients with planned elective major surgery and SBP ≥180 mmHg or DBP ≥110 mmHg, deferring surgery may be considered. • For patients undergoing surgery, abrupt pre-operative discontinuation of beta-blockers or clonidine is potentially harmful. • Beta-blockers should not be started on the day of surgery in beta-blocker-naïve patients. • Patients with intraoperative hypertension should be managed with IV medications until such time as oral medications can be resumed.
American Diabetes Association: **Standards of Medical Care in Diabetes (2023)**[39]	Hypertension/blood pressure control • Blood pressure should be measured at every routine visit. When possible, patients found to have elevated blood pressure (systolic blood pressure 120 to 129 mmHg and diastolic <80 mmHg) should have blood pressure confirmed using multiple readings, including measurements on a separate day, to diagnose hypertension. Patients with blood pressure ≥180/110 and cardiovascular disease could be diagnosed with hypertension at a single visit.

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	• All hypertensive patients with diabetes should monitor their blood pressure at home. • For patients with diabetes and hypertension, blood pressure targets should be individualized through a shared decision-making process that addresses cardiovascular risk, potential adverse effects of antihypertensive medications, and patient preferences. • Individuals with diabetes and hypertension qualify for antihypertensive drug therapy when the blood pressure is persistently elevated ≥130/80 mmHg. The on-treatment target blood pressure goal is <130/80 mmHg, if it can be safely attained. • In pregnant patients with diabetes and preexisting hypertension, a blood pressure target of 110 to 135/85 is suggested in the interest of reducing the risk for accelerated maternal hypertension and minimizing impaired fetal growth. • For patients with blood pressure >120/80, lifestyle intervention consists of weight loss when indicated, a Dietary Approaches to Stop Hypertension (DASH)-style eating pattern including reducing sodium and increasing potassium intake, moderation of alcohol intake, and increased physical activity. • Patients with confirmed office-based blood pressure ≥130/80 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of pharmacologic therapy to achieve blood pressure goals. • Patients with confirmed office-based blood pressure ≥160/100 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of two drugs or a single pill combination of drugs demonstrated to reduce cardiovascular events in patients with diabetes. • Treatment for hypertension should include drug classes demonstrated to reduce cardiovascular events in patients with diabetes (ACE inhibitors, angiotensin receptor blockers, thiazide-like diuretics, or dihydropyridine calcium channel blockers). ACE inhibitors or angiotensin receptor blockers are recommended first-line therapy for hypertension in people with diabetes and coronary artery disease. • Multiple-drug therapy is generally required to achieve blood pressure targets (but not a combination of ACE inhibitors and angiotensin receptor blockers). • An ACE inhibitor or angiotensin receptor blocker, at the maximum tolerated dose indicated for blood pressure treatment, is the recommended first-line treatment for hypertension in patients with diabetes and urinary albumin–to–creatinine ratio ≥300 mg/g creatinine or 30 to 299 mg/g creatinine. If one class is not tolerated, the other should be substituted. • For patients treated with an ACE inhibitor, angiotensin receptor blocker, or diuretic, serum creatinine/estimated glomerular filtration rate and serum potassium levels should be monitored at least annually. • Patients with hypertension who are not meeting blood pressure targets on three classes of antihypertensive medications (including a diuretic) should be considered for mineralocorticoid receptor antagonist therapy. <u>Chronic kidney disease</u> • At least once a year, assess urinary albumin (e.g., spot urinary albumin–to–creatinine ratio) and estimated glomerular filtration rate in patients with type 1 diabetes with duration of five or more years and in all patients with type 2 diabetes. • In people with established diabetic kidney disease, urinary albumin (e.g., spot urinary albumin-to-creatinine ratio) and estimated glomerular filtration rate should be monitored one to four times per year depending on the stage of the disease. Optimize glucose control to reduce the risk or slow the progression of chronic kidney disease (CKD). • For patients with type 2 diabetes and diabetic kidney disease, use of a sodium-

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	glucose cotransporter 2 inhibitor in patients with an estimated glomerular filtration rate ≥20 mL/min/1.73 m^2 and urinary albumin ≥200 mg/g creatinine is recommended to reduce CKD progression and cardiovascular events. • For patients with type 2 diabetes and diabetic kidney disease, use of a sodium–glucose cotransporter 2 inhibitor is recommended to reduce chronic kidney disease progression and cardiovascular events in patients with an estimated glomerular filtration rate ≥20 mL/min/1.73 m^2 and urinary albumin ranging from normal to 200 mg/g creatinine. • In people with type 2 diabetes and diabetic kidney disease, consider use of sodium–glucose cotransporter 2 inhibitors (if estimated glomerular filtration rate is ≥20 mL/min/1.73 m^2), a glucagon-like peptide 1 agonist, or a nonsteroidal mineralocorticoid receptor antagonist (if estimated glomerular filtration rate is ≥25 mL/min/1.73 m^2) additionally for cardiovascular risk reduction. • In people with chronic kidney disease and albuminuria who are at increased risk for cardiovascular events or chronic kidney disease progression, a nonsteroidal mineralocorticoid receptor antagonist shown to be effective in clinical trials is recommended to reduce chronic kidney disease progression and cardiovascular events. • Optimize blood pressure control and reduce blood pressure variability to reduce the risk or slow the progression of CKD. • Do not discontinue renin-angiotensin system blockade for minor increases in serum creatinine (≤30%) in the absence of volume depletion. • For people with nondialysis-dependent stage 3 or higher CKD, dietary protein intake should be a maximum of 0.8 g/kg body weight per day (the recommended daily allowance). For patients on dialysis, higher levels of dietary protein intake should be considered, since protein energy wasting is a major problem in some dialysis patients. • In nonpregnant patients with diabetes and hypertension, either an ACE inhibitor or an angiotensin receptor blocker is recommended for those with modestly elevated urinary albumin–to–creatinine ratio (30 to 299 mg/g creatinine) and is strongly recommended for those with urinary albumin–to–creatinine ratio ≥300 mg/g creatinine and/or estimated glomerular filtration rate <60 mL/min/1.73 m^2. • Periodically monitor serum creatinine and potassium levels for the development of increased creatinine and hyperkalemia when ACE inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists are used, or hypokalemia when diuretics are used. • An ACE inhibitor or an angiotensin receptor blocker is not recommended for the primary prevention of CKD in patients with diabetes who have normal blood pressure, normal urinary albumin–to–creatinine ratio (<30 mg/g creatinine), and normal estimated glomerular filtration rate. • Patients should be referred for evaluation by a nephrologist if they have continuously increasing urinary albumin levels and/or continuously decreasing estimated glomerular filtration rate and an estimated glomerular filtration rate <30 mL/min/1.73 m^2. • Promptly refer to a nephrologist for uncertainty about the etiology of kidney disease, difficult management issues, and rapidly progressing kidney disease.

*Agent not available in the United States.

III. Indications

The FDA-approved indications for the angiotensin II receptor antagonists are noted in Tables 3 and 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively on the results of such clinical trials.

Table 3. FDA-Approved Indications for the Angiotensin II Receptor Antagonists-Single Entity Agents[3-19]

Indication(s)	Single Entity Agents						
	Azil-sartan	Cande-sartan	Irbe-sartan	Lo-sartan	Olme-sartan	Telmi-sartan	Val-sartan
Cardiovascular Risk Reduction							
Reduce the risk of cardiovascular mortality in clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction							✔
Reduce the risk of myocardial infarction, stroke, or death from cardiovascular causes in patients ≥55 years of age at high risk of developing major cardiovascular events who are unable to take an angiotensin converting enzyme inhibitor						✔	
Reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy				✔ *			
Heart Failure							
Heart failure (New York Heart Association functional class II to IV)							✔
Heart failure (New York Heart Association functional class II to IV) in adults with left ventricular systolic dysfunction (ejection fraction ≤40%) to reduce cardiovascular death and to reduce heart failure hospitalizations		✔					
Hypertension							
Hypertension, alone or in combination with other antihypertensive agents	✔	✔	✔	✔	✔	✔	✔
Nephropathy in Type 2 Diabetic Patients							
Diabetic nephropathy with an elevated serum creatinine and proteinuria (>300 mg/day) in patients with type 2 diabetes and hypertension			✔	✔			

*There is evidence that this benefit does not apply to Black patients.

Table 4. FDA-Approved Indications for the Angiotensin II Receptor Antagonists-Combination Products[3-19]

Indication(s)	Combination Products								
	Azilsartan and chlorthali-done	Candesartan and HCTZ	Irbesartan and HCTZ	Losartan and HCTZ	Olmesartan and Amlodipine and HCTZ	Olmesartan and HCTZ	Telmisartan and Amlodipine	Telmisartan and HCTZ	Valsartan and HCTZ
Cardiovascular Risk Reduction									
Reduce the risk of stroke in				✔ *					

Indication(s)	Combination Products								
	Azilsartan and chlorthali-done	**Candesartan and HCTZ**	**Irbesartan and HCTZ**	**Losartan and HCTZ**	**Olmesartan and Amlodipine and HCTZ**	**Olmesartan and HCTZ**	**Telmisartan and Amlodipine**	**Telmisartan and HCTZ**	**Valsartan and HCTZ**
patients with hypertension and left ventricular hypertrophy									
Hypertension									
Hypertension	✔	✔ †	✔	✔ §	✔ †	✔ †	✔ ‡	✔ †	✔

*There is evidence that this benefit does not apply to Black patients.
†This fixed dose combination is not indicated for initial therapy.
‡May be used alone or in combination with other antihypertensive agents.
§This fixed dose combination is not indicated for initial therapy, except when the hypertension is severe enough that the value of achieving prompt blood pressure control exceeds the risk of initiating combination therapy in these patients.
HCTZ=hydrochlorothiazide

IV. Pharmacokinetics

The pharmacokinetic parameters of the angiotensin II receptor antagonists are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Angiotensin II Receptor Antagonists[20]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Azilsartan	60	>99	Liver (% not reported)	Feces (55) Renal (42)	11
Candesartan	15	>99	Intestinal wall (>99)	Feces (67) Renal (33)	9
Irbesartan	60 to 80	90	Liver (50 to 70)	Feces (65) Renal (20)	11 to 15
Losartan	25 to 35	99	Liver (14)	Feces (50 to 60) Renal (13 to 35)	2
Olmesartan	26	99	Intestinal wall (100)	Feces (50 to 65) Renal (35 to 50)	13
Telmisartan	42 to 58	>99	Liver (<3)	Feces (97)	24
Valsartan	25	95	Liver, minimal (% not reported)	Feces (83) Renal (13)	6 to 9
Combination Products					
Azilsartan and Chlorthalidone	60/not reported	>99/75	Liver (% not reported)/ Not reported	Feces (55) Renal (42)/ Renal, major (% not reported)	12/45
Candesartan and HCTZ	15/70	>99/40	Liver, minimal (% not reported)/ Not metabolized	Feces (67) Renal (26)/ Renal (61)	5.1 to 10.5/ 5.6 to 14.8
Irbesartan and HCTZ	60 to 80/not reported	90/40	Liver (% not reported)/ Not metabolized	Feces, majority (% not reported) Renal (20)/ Renal (61)	10 to 12/ 11 to 15
Losartan and HCTZ	33/not reported	Not reported/not reported	Systemic (% not reported)/ Not metabolized	Feces (60) Renal (35)/ Renal (% not reported)	2/ 5.6 to 14.8
Olmesartan and amlodipine and HCTZ	26/ 64 to 90/ Not reported	99/ 93/ Not reported	Intestinal wall, extensive/ Liver (90)/ Not reported	Feces (50 to 65) Renal (35 to 50)/ Renal (10)/ Renal (61)	13/ 30 to 50/ 5.6 to 14.8
Olmesartan and HCTZ	26/Not reported	99/Not reported	Hydrolysis (complete)/Not metabolized	Feces (% not reported) Renal (35 to 50)/ Renal (61)	13/ 5.6 to 14.8
Telmisartan and amlodipine	64 to 90/ 42 to 58	99.5/93	Hepatic, minimal (% not reported)/ Hepatic (90)	Feces (>97) Renal (<1)/ Feces (20 to 25) Renal (10)	24/ 30 to 50
Telmisartan and HCTZ	42 to 58/Not reported	Not reported/Not reported	Not reported/Not reported	Feces (97)/ Renal (61)	24/ 5.6 to 14.8
Valsartan and HCTZ	25/70	95/40 to 70	Liver, minimal (% not reported)/ Not reported	Feces (83) Renal (13)/ Renal (70)	6 to 9/ 10 to 12

HCTZ=hydrochlorothiazide

V. Drug Interactions

Major drug interactions with the angiotensin II receptor antagonists are listed in Table 6.

Table 6. Major Drug Interactions with the Angiotensin II Receptor Antagonists[20]

Generic Name(s)	Interaction	Mechanism
ARBs (azilsartan, candesartan, irbesartan, losartan, olmesartan, telmisartan, valsartan)	ACE inhibitors	Concurrent use of angiotensin converting enzyme inhibitors and ARBs may result in increased risk of adverse events (i.e., hypotension, syncope, hyperkalemia, changes in renal function, acute renal failure).
ARBs (azilsartan, irbesartan)	Fluconazole	Concurrent use of fluconazole and selected ARBs may result in increased exposure of ARB and increased risk of toxicity.
ARBs (azilsartan, candesartan, irbesartan, losartan, olmesartan, telmisartan, valsartan)	Lithium	Angiotensin II receptor antagonists may decrease lithium renal excretion by enhancing its reabsorption. Lithium levels may increase, resulting in an increase in pharmacologic and toxic effects of lithium.
ARBs (azilsartan, candesartan, irbesartan, losartan, olmesartan, telmisartan, valsartan)	Trimethoprim	Angiotensin II receptor antagonists and trimethoprim may act additively or synergistically to inhibit renal excretion of potassium, increasing the risk of hyperkalemia.
ARBs (azilsartan, candesartan, irbesartan, losartan, olmesartan, telmisartan, valsartan	Aliskiren	Concurrent use of aliskiren and ARBs may result in an increased risk of hyperkalemia, renal impairment, and hypotension.
Telmisartan	Digoxin	Concurrent use of digoxin and telmisartan may result in an increased risk of digoxin toxicity (nausea, vomiting, arrhythmias).
Dihydropyridines (amlodipine)	HIV protease inhibitors	Pharmacologic effects of amlodipine may be enhanced by protease inhibitors.
Dihydropyridines (amlodipine)	Imidazoles	Imidazoles may increase the plasma concentrations and pharmacologic effects of amlodipine.
Thiazide diuretics (HCTZ)	Dofetilide	Thiazide diuretics may induce hypokalemia which may increase the risk of torsades de pointes.
Thiazide diuretics (HCTZ)	Lithium	Thiazide diuretics decrease the renal clearance of lithium which leads to increased serum lithium levels. Lithium toxicity has occurred.
Thiazide diuretics (HCTZ)	Diazoxide	The combination of diazoxide with a thiazide diuretic may lead to hyperglycemia though an unknown mechanism; therefore the combination should be avoided.
Thiazide diuretics (HCTZ)	Digitalis glycosides	Diuretic-induced electrolyte disturbances may predispose the patient to digitalis-induced cardiac arrhythmias.

ACE inhibitor=angiotensin converting enzyme inhibitor, ARB=angiotensin II receptor antagonist, HCTZ=hydrochlorothiazide, HIV=human immunodeficiency virus

VI. Adverse Drug Events

The most common adverse drug events reported with the angiotensin II receptor antagonists are listed in Table 7. The most common adverse drug events reported with amlodipine and hydrochlorothiazide are listed in Table 8. The boxed warning for the angiotensin II receptor antagonists is listed in Table 9.

Table 7. Adverse Drug Events (%) Reported with the Combination Angiotensin II Receptor Antagonists-Single Entity Agents[3-19]

Adverse Events	Single Entity Agents						
	Azilsartan	Candesartan	Irbesartan	Losartan	Olmesartan	Telmisartan	Valsartan
Cardiovascular							
Chest pain	-	>1	≥1	≥1	>0.5	1	-
Hypertension	-	-	<1	-	-	-	-
Hypotension	-	-	<1	<1	-	-	<1
Orthostatic hypotension	-	-	✔	-	-	-	-
Tachycardia	-	≥0.5	≥1	<1	>0.5	>0.3	-
Central Nervous System							
Anxiety/nervousness	-	≥0.5	≥1	<1	-	>0.3	>0.2
Depression	-	≥0.5	<1	<1	-	>0.3	-
Dizziness	≥0.3	4	≥1	4	3	1	>1
Dizziness, postural	≥0.3	-	-	-	-	-	-
Fatigue	-	>1	4	-	>0.5	1	2
Headache	-	≥1	≥1	≥1	>1	1	>1
Insomnia	-	-	-	1	>0.5	>0.3	>0.2
Dermatological							
Rash	-	≥0.5	≥1	<1	>0.5	>0.3	>0.2
Gastrointestinal							
Abdominal pain	-	>1	≥1	≥1	>0.5	1	2
Diarrhea	2	>1	3	2	>1	3	>1
Dyspepsia/heartburn	-	≥0.5	2	1	>0.5	1	>0.2
Nausea/vomiting	≥0.3	>1	≥1	≥1	>0.5	1	>1
Genitourinary							
Albuminuria	-	>1	-	-	-	-	-
Hematuria	-	≥0.5	-	-	>1	-	-
Urinary tract infection	-	-	≥1	<1	>0.5	1	-
Laboratory Test Abnormalities							
Creatine phosphokinase increased	-	≥0.5	-	-	>1	-	-
Decreased hematocrit	0.4	-	-	-	-	-	-
Decreased hemoglobin	0.2	-	-	-	-	-	-
Decreased red blood counts	0.3	-	-	-	-	-	-
Hyperglycemia	-	≥0.5	-	-	>1	-	-
Hyperkalemia	-	✔	✔	✔	-	-	✔
Hypertriglyceridemia	-	≥0.5	-	-	>1	-	-
Musculoskeletal							
Arthralgia	-	>1	-	<1	>0.5	>0.3	>1
Muscle cramp	-	-	-	1.1	-	-	>0.2
Muscle spasm	≥0.3	-	-	-	-	-	-

Adverse Events	Single Entity Agents						
	Azilsartan	Candesartan	Irbesartan	Losartan	Olmesartan	Telmisartan	Valsartan
Myalgia	-	≥0.5	-	1	>0.5	1	>0.2
Pain (includes back and leg)	-	3	≥1	1 to 2	>1	1 to 3	>0.2
Trauma	-	-	2	-	-	-	-
Respiratory							
Bronchitis	-	>1	-	<1	>1	>0.3	-
Cough	≥0.3	>1	3	3	-	1	>1
Influenza/influenza-like symptoms	-	-	≥1	<1	>1	1	-
Nasal congestion	-	-	-	2	-	-	-
Pharyngitis	-	2	≥1	≥1	>1	1	>1
Rhinitis	-	2	≥1	<1	>1	>0.3	>1
Sinus disorder	-	-	≥1	2	-	-	-
Sinusitis	-	>1	-	1	>1	3	>1
Upper respiratory tract infection	-	6	9	8	>1	7	>1
Miscellaneous							
Allergic reactions	-	✔	✔	✔	✔	✔	✔
Angioedema	-	✔	✔	✔	✔	✔	✔
Asthenia	≥0.3	-	-	-	-	-	-
Edema	-	>1	≥1	≥1	>0.5	1	>1
Fatigue	≥0.3	-	-	-	-	-	-
Inflicted injury	-	-	-	-	>1	-	-
Viral infection	-	-	-	-	-	-	3

✔ Percent not specified
- Event not reported

Table 8. Adverse Drug Events (%) Reported with the Combination Angiotensin II Receptor Antagonists-Combination Products[3-19]

Adverse Event	Azilsartan and Chlorthalidone	Candesartan and HCTZ	Irbesartan and HCTZ	Losartan and HCTZ	Olmesartan and Amlodipine and HCTZ	Olmesartan and HCTZ	Telmisartan and Amlodipine	Telmisartan and HCTZ	Valsartan and HCTZ
Cardiovascular									
Abnormal electrocardiogram	-	≥0.5	-	-	-	-	-	-	-
Angina	-	<0.5	-	-	-	-	-	-	-
Bradycardia	-	≥0.5	-	-	-	-	-	-	-
Chest pain	-	≥0.5	2	-	-	>1	-	-	>0.2
Extrasystoles	-	≥0.5	-	-	-	-	-	-	-
Hypotension	1.7	-	0.6 to 0.9	0.6	-	-	<2.0	<2	>0.2 to 1.0
Myocardial infarction	-	<0.5	-	-	-	-	-	-	-
Palpitations	-	≥0.5	-	1.4	-	-	-	-	>0.2
Syncope	0.3	-	-	-	1	-	<2.0	-	✔
Tachycardia	-	≥0.5	1	-	-	-	-	<2	>0.2
Central Nervous System									
Anxiety	-	≥0.5	≥1	-	-	-	-	-	>0.2
Asthenia	-	≥0.5	-	≥1	-	-	-	-	>0.2
Depression	-	≥0.5	-	-	-	-	-	-	✔
Dizziness	8.9	2.9	1 to 8	5.7	-	9	3.0	1 to 7	>0.2 to 6.0

Adverse Event	Azilsartan and Chlorthalidone	Candesartan and HCTZ	Irbesartan and HCTZ	Losartan and HCTZ	Olmesartan and Amlodipine and HCTZ	Olmesartan and HCTZ	Telmisartan and Amlodipine	Telmisartan and HCTZ	Valsartan and HCTZ
Headache	-	2.9	1.0 to 5.5	≥1	6.4	>2	-	≥2	-
Hypesthesia	-	≥0.5	-	-	-	-	-	-	-
Insomnia	-	≥0.5	-	-	-	-	-	-	>0.2
Nervousness	-	-	≥1	-	-	-	-	-	-
Paresthesia	-	≥0.5	-	-	-	-	-	-	>0.2
Somnolence	-	-	-	-	-	-	-	-	>0.2
Vertigo	-	≥0.5	-	-	-	>1	-	-	>0.2
Dermatological									
Alopecia	-	-	-	-	-	✔	-	-	✔
Dermatitis	-	≥0.5	-	-	-	-	-	-	-
Eczema	-	≥0.5	-	-	-	-	-	-	-
Pruritus	-	≥0.5	-	-	-	✔	-	-	✔
Rash	-	≥0.5	≥1	1.4	-	>1	-	<2	>0.2
Sweating	-	≥0.5	-	-	-	-	-	-	>0.2
Urticaria	-	-	✔	-	-	✔	-	-	-
Gastrointestinal									
Abdominal pain	-	≥0.5	2	1.2	-	>1	-	<2	>0.2
Constipation	-	-	-	-	-	-	-	-	✔
Diarrhea	-	≥0.5	≥1	≥1	2.6	>1	-	3	>0.2
Dry mouth	-	-	-	-	-	-	-	-	>0.2
Dyspepsia	-	≥0.5	2	-	-	>1	-	<2	>0.2
Flatulence	-	-	-	-	-	-	-	-	>0.2
Gastritis	-	≥0.5	-	-	-	-	-	-	-
Gastroenteritis	-	≥0.5	-	-	-	>1	-	-	>0.2
Hepatic function abnormal	-	≥0.5	-	-	-	-	-	-	-
Hepatitis	-	-	✔	-	-	-	-	-	✔
Nausea	-	≥0.5	3	≥1	3.0	3	-	2	>0.2
Vomiting	-	≥0.5	3	-	-	✔	-	<2	>0.2
Laboratory Test Abnormalities									
Bilirubin increased	-	✔	-	✔	-	-	-	✔	-
Blood urea nitrogen increased	-	≥0.5	-	0.6	-	1.3	-	2.8	>0.2
Creatine phosphokinase increased	-	≥0.5	-	-	-	>1	-	-	-
Hematocrit decreased	-	✔	-	✔	-	0.4	-	0.6	-
Hemoglobin decreased	-	✔	-	✔	-	-	-	1.2	-
Hyperglycemia	-	≥0.5	-	-	-	>1	-	-	-
Hyperkalemia	-	-	0.2 to 1.2	-	-	✔	-	-	✔
Hyperlipidemia	-	-	-	-	-	>1	-	-	-
Hyperuricemia	-	≥0.5	-	-	-	4	-	-	-
Hypokalemia	-	≥0.5	0.6 to 0.9	-	-	-	-	<2	-
Serum creatinine increased	-	✔	-	0.8	-	-	-	1.4	-
Thrombocytopenia	-	-	-	✔	-	-	-	-	-
Transaminase levels increased	-	≥0.5	-	✔	-	>1	-	✔	✔
Musculoskeletal									
Arthralgia	-	≥0.5	-	-	-	>1	-	-	>0.2

Adverse Event	Azilsartan and Chlorthalidone	Candesartan and HCTZ	Irbesartan and HCTZ	Losartan and HCTZ	Olmesartan and Amlodipine and HCTZ	Olmesartan and HCTZ	Telmisartan and Amlodipine	Telmisartan and HCTZ	Valsartan and HCTZ
Arthritis	-	≥0.5	-	-	-	>1	-	-	-
Arthrosis	-	≥0.5	-	-	-	-	-	-	-
Back pain	-	3.3	-	2.1	-	>1	2.2	<2	>0.2
Joint swelling	-	-	-	-	2.1	-	-	-	-
Leg cramps	-	≥0.5	-	-	-	-	-	-	-
Muscle cramps	-	-	≥1	-	-	-	-	-	>0.2
Muscle spasms	-	-	-	-	3.1	-	-	-	-
Muscle weakness	-	-	-	-	-	-	-	-	✔
Musculoskeletal pain	-	-	6	-	-	-	-	-	-
Myalgia	-	≥0.5	-	-	-	>1	-	-	>0.2
Pain in extremity	-	-	-	-	-	-	-	-	>0.2
Rhabdomyolysis	-	-	✔	-	-	✔	-	-	✔
Sciatica	-	≥0.5	-	-	-	-	-	-	-
Respiratory									
Bronchitis	-	≥0.5	-	≥1	-	-	-	<2	>0.2
Bronchospasm	-	-	-	-	-	-	-	-	✔
Cough	-	≥0.5	≥1	2.6	-	>1	-	≥2	>0.2
Dyspnea	-	≥0.5	-	-	-	-	-	-	>0.2
Epistaxis	-	≥0.5	-	-	-	-	-	-	✔
Nasal congestion	-	-	-	-	-	-	-	-	>0.2
Nasopharyngitis	-	-	-	-	3.5	-	-	2.4	-
Pharyngitis	-	≥0.5	≥1	≥1	-	-	-	<2	✔
Pharyngolaryngeal pain	-	-	-	-	-	-	-	-	>0.2
Rhinitis	-	≥0.5	≥1	-	-	-	-	-	-
Sinus abnormality	-	-	≥1	-	-	-	-	-	-
Sinus congestion	-	-	-	-	-	-	-	-	>0.2
Sinusitis	-	≥0.5	-	1.2	-	-	-	4	>0.2
Upper respiratory tract infection	-	3.6	≥1	6.1	2.8	7	-	8	>0.2
Miscellaneous									
Abnormal vision	-	-	-	-	-	-	-	-	✔
Acute renal failure	-	-	-	-	-	✔	-	-	-
Allergy	-	-	1	-	-	-	-	-	-
Anaphylaxis	-	-	-	-	-	-	-	-	✔
Angioedema	-	<0.5	✔	✔	-	✔	-	-	✔
Appetite increased	-	-	-	-	-	-	-	-	✔
Conjunctivitis	-	≥0.5	-	-	-	-	-	-	-
Cystitis	-	≥0.5	-	-	-	-	-	-	-
Dehydration	-	-	-	-	-	-	-	-	✔
Dysuria	-	-	-	-	-	-	-	-	✔
Edema	-	-	3	1.3	-	-	<2.0	-	-
Erectile dysfunction	-	-	-	-	-	-	-	-	>0.2
Facial edema	-	-	-	-	-	✔	-	-	-
Fatigue	2.0	≥0.5	6	≥1	4.2		-	3	>0.2
Fever	-	-	-	-	-	-	-	-	>0.2

Adverse Event	Azilsartan and Chlorthalidone	Candesartan and HCTZ	Irbesartan and HCTZ	Losartan and HCTZ	Olmesartan and Amlodipine and HCTZ	Olmesartan and HCTZ	Telmisartan and Amlodipine	Telmisartan and HCTZ	Valsartan and HCTZ
Flushing	-	-	-	-	-	-	-	-	✔
Gout	-	-	-	-	-	-	-	-	✔
Hematuria	-	≥0.5	-	-	-	>1	-	-	-
Inflicted injury	-	≥0.5	-	-	-	-	-	-	-
Influenza-like symptoms	-	2.5	3	-	-	-	-	2	>0.2
Infection	-	≥0.5	-	-	-	-	-	-	-
Libido decreased	-	-	-	-	-	-	-	-	✔
Pain	-	≥0.5	-	-	-	-	-	≥2	-
Peripheral edema	-	≥0.5	-	-	7.7	>1	4.8	-	>0.2
Pollakiuria	-	-	-	-	-	-	-	-	>0.2
Renal impairment	-	-	-	-	-	-	-	-	✔
Sunburn	-	-	-	-	-	-	-	-	✔
Tinnitus	-	≥0.5	-	-	-	-	-	-	>0.2
Urinary tract infection	-	≥0.5	≥1	-	2.4	>2	-	≥2	-
Urination abnormal	-	-	2	-	-	-	-	-	>0.2
Vasculitis	-	-	-	-	-	-	-	-	✔
Viral infection	-	≥0.5	-	-	-	-	-	-	✔

✔ Percent not specified
- Event not reported
HCTZ=hydrochlorothiazide

Table 9. Boxed Warning for the Angiotensin II Receptor Antagonists[19]

WARNING
When pregnancy is detected, discontinue therapy as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus.

VII. Dosing and Administration

The usual dosing regimens for the angiotensin II receptor antagonists are listed in Table 10.

Table 10. Usual Dosing Regimens for the Angiotensin II Receptor Antagonists[3-20]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Azilsartan	Hypertension: Tablet: initial, 40 or 80 mg once daily; maintenance, 80 mg once daily	Safety and efficacy in children have not been established.	Tablet: 40 mg 80 mg
Candesartan	Heart Failure: Tablet: initial, 4 mg once daily; maintenance, 32 mg once daily Hypertension: Tablet: initial, 16 mg once daily when used as monotherapy in patients who are not volume-depleted; maintenance: 8 to 32 mg/day in a single or divided dose(s)	Hypertension in children 1 to 6 years of age: Tablet: initial, 0.2 mg/kg/day; maintenance, 0.05 to 0.4 mg/kg/day Hypertension in children 7 to 17 years of age and <50 kg: Tablet: initial, 4 to 8 mg/day; maintenance, 2 to 16 mg/day Hypertension in children 7 to 17 years of age and >50 kg: Tablet: initial, 8 to 16 mg/day; maintenance, 4 to 32 mg/day Safety and efficacy in children with heart failure have not been established.	Tablet: 4 mg 8 mg 16 mg 32 mg
Irbesartan	Diabetic nephropathy: Tablet: 300 mg once daily Hypertension: Tablet: initial, 150 mg once daily in patients who are not volume-depleted; maximum, 300 mg once daily	Safety and efficacy in children have not been established.	Tablet: 75 mg 150 mg 300 mg
Losartan	Cerebrovascular risk reduction (hypertension and left ventricular hypertrophy): Tablet: initial, 50 mg once daily; maintenance, 100 mg once daily Diabetic nephropathy: Tablet: initial, 50 mg once daily; maintenance, dose should be increased to 100 mg once daily based on blood pressure response	Hypertension in children ≥6 years of age: Tablet: initial, 0.7 mg/kg once daily (up to 50 mg total); maximum, >1.4 mg/kg/day (or in excess of 100 mg) have not been studied Safety and efficacy in children <6 years of age have not been established.	Tablet: 25 mg 50 mg 100 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Hypertension: Tablet: initial, 50 mg once daily in patients who are not volume-depleted; maintenance, 25 to 100 mg/day in a single or divided dose(s)		
Olmesartan	Hypertension: Tablet: initial, 20 mg once daily when used as monotherapy in patients who are not volume depleted; maximum, 40 mg once daily	Hypertension in children 6 to 16 years of age and 20 to <35 kg: Tablet: initial, 10 mg once daily; maximum, 20 mg once daily Hypertension in children 6 to 16 years of age ≥35 kg: Tablet: initial, 20 mg once daily; maximum, 40 mg once daily Safety and efficacy in children <6 years of age have not been established.	Tablet: 5 mg 20 mg 40 mg
Telmisartan	Cardiovascular risk reduction: Tablet: 80 mg once daily Hypertension: Tablet: initial, 40 mg once daily; maximum: 80 mg per day	Safety and efficacy in children have not been established.	Tablet: 20 mg 40 mg 80 mg
Valsartan	Cardiovascular risk reduction (post-myocardial infarction): Tablet: initial, 20 mg twice daily; maintenance: 160 mg twice daily Heart Failure: Tablet: Initial, 40 mg twice daily; maintenance, up titrate to 80 to 160 mg twice daily; maximum, 320 mg in divided doses Hypertension: Tablet: initial, 80 to 160 mg once daily when used as monotherapy in patients who are not volume depleted; maintenance, 80 to 320 mg once daily	Hypertension in children 1 to 16 years of age: Tablet: initial, 1 mg/kg once daily (up to 40 mg total) administered as a tablet or suspension; maximum, >4 mg/kg/day (or in excess of 160 mg) have not been studied Safety and efficacy in children with hypertension <1 years of age, or with heart failure, or for cardiovascular risk reduction have not been established.	Tablet: 40 mg 80 mg 160 mg 320 mg
Combination Products			
Azilsartan and chlorthalidone	Hypertension: Tablet: initial, 40-12.5 mg once daily; maintenance, 40-25 mg once daily; maximum, 40-25 mg /day	Safety and efficacy in children have not been established.	Tablet: 40-12.5 mg 40-25 mg
Candesartan and HCTZ	Hypertension: Tablet: 16-12.5 to 32-25 mg/day	Safety and efficacy in children have not been established.	Tablet: 16-12.5 mg 32-12.5 mg 32-25 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Irbesartan and HCTZ	Hypertension: Tablet: initial, 150-12.5 mg once daily; maximum, 300-25 mg once daily	Safety and efficacy in children have not been established.	Tablet: 150-12.5 mg 300-12.5 mg
Losartan and HCTZ	Cerebrovascular risk reduction (hypertension and left ventricular hypertrophy): Tablet: initial, 50-12.5 mg once daily; maintenance, 100-12.5 mg once daily; maximum, 100-25 mg once daily Hypertension: Tablet: initial, 50-12.5 mg once daily; maintenance, 100-12.5 mg once daily; maximum, 100-25 mg once daily	Safety and efficacy in children have not been established.	Tablet: 50-12.5 mg 100-12.5 mg 100-25 mg
Olmesartan and amlodipine and HCTZ	Hypertension: Tablet: maximum, 40-10-25 mg once daily	Safety and efficacy in children have not been established.	Tablet: 20-5-12.5 mg 40-5-12.5 mg 40-5-25 mg 40-10-12.5 mg 40-20-25 mg
Olmesartan and HCTZ	Hypertension: Tablet: 20-12.5 to 40-25 mg/day	Safety and efficacy in children have not been established.	Tablet: 20-12.5 mg 40-12.5 mg 40-25 mg
Telmisartan and amlodipine	Hypertension: Tablet: initial, 40-5 or 80-5 mg once daily; maintenance, titrate as needed; maximum , 80-10 mg once daily	Safety and efficacy in children have not been established.	Tablet: 40-5 mg 40-10 mg 80-5 mg 80-10 mg
Telmisartan and HCTZ	Hypertension: Tablet: 40-12.5 to 80-25 mg once daily	Safety and efficacy in children have not been established.	Tablet: 40-12.5 mg 80-12.5 mg 80-25 mg
Valsartan and HCTZ	Hypertension: Tablet: 80-12.5 to 320-25 mg once daily	Safety and efficacy in children have not been established.	Tablet: 80-12.5 mg 160-12.5 mg 160-25 mg 320-12.5 mg 320-25 mg

HCTZ=hydrochlorothiazide

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the angiotensin II receptor antagonists are summarized in Table 11.

Table 11. Comparative Clinical Trials with the Angiotensin II Receptor Antagonists

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cardiovascular Risk Reduction				
Pfeffer et al.[40] (2003) VALIANT Captopril 50 mg TID vs valsartan 160 mg BID vs valsartan 80 mg BID and captopril 50 mg TID	DB, MC, RCT Patients ≥18 years of age with an acute MI that was complicated by clinical or radiologic signs of heart failure and/or evidence of left ventricular systolic dysfunction	N=14,703 24.7 months	Primary: All-cause mortality Secondary: Death from cardiovascular causes, recurrent MI, hospitalization for heart failure	Primary: No significant difference in all-cause mortality was reported between valsartan monotherapy and captopril monotherapy (P=0.98). No significant difference in all-cause mortality was observed between valsartan plus captopril combination therapy and captopril monotherapy (P=0.73). Secondary: The rate of death from cardiovascular causes, reinfarction, or hospitalization for heart failure was not significantly different between valsartan and captopril monotherapy (P=0.20). The rate of death from cardiovascular causes, reinfarction, or hospitalization for heart failure was not significantly different between valsartan and captopril combination therapy and captopril monotherapy (P=0.37). Combination therapy had the most drug-related adverse events. With monotherapy, hypotension and renal dysfunction were more common in the valsartan group and cough, rash, and taste disturbance were more common in the captopril group.
Dickstein et al.[41] (2002) OPTIMAAL Captopril 50 mg TID vs losartan 50 mg QD	DB, MC, PG, RCT Patients ≥50 years with an acute MI and signs or symptoms of heart failure during the acute phase or a new Q-wave anterior infarction or	N=5,477 2.7 years (mean)	Primary: All-cause mortality Secondary: Composite of sudden cardiac death or resuscitated cardiac arrest	Primary: No significant difference in all-cause mortality was reported between patients receiving losartan and captopril (18 vs 16%, respectively; RR, 1.13; 95% CI, 0.99 to 1.28; P=0.07). Secondary: No significant difference in sudden cardiac death or resuscitated cardiac arrest was reported between patients receiving losartan and captopril (9 vs 7%; RR, 1.19; 95% CI, 0.98 to 1.43; P=0.07).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	reinfarction			Losartan was significantly better tolerated than captopril, with fewer patients discontinuing study medication (17 vs 23%; P<0.0001).
Graham et al.[42] (2014) Olmesartan vs other ARBs	Cohort, RETRO Medicare patients (age 65 years or older) who filled at least one ARB prescription and had no recorded prescription for an ACE inhibitor or ARB 6 months prior to initiating a study drug. Results also stratified by diabetes or no diabetes	N=882,727 Mean duration of study drug use was 130 days	Primary: Acute MI, stroke, and all-cause mortality enriched for acute cardiovascular death Secondary: Not reported	Primary: In the combined study population, there was no difference in the HRs for acute MI or stroke. The HR for death was reduced for olmesartan compared with other ARB users (HR, 0.82; 95% CI, 0.73 to 0.93; P=0.002). In strata defined by presence or absence of diabetes, there was no difference in risk between users of olmesartan and other ARBs for any study endpoint at lower doses of therapy, regardless of duration of use. With high-dose therapy, the risk of acute MI was nonsignificantly increased in diabetic patients treated for 6 months or longer with olmesartan. For nondiabetic patients, the risk of acute MI was statistically significantly reduced with high-dose olmesartan over all durations combined. There was no effect of dose or duration on stroke risk with olmesartan in diabetic or nondiabetic patients. Mortality risk was increased in diabetic patients treated with high-dose olmesartan for 6 months or longer (HR, 2.03; 95% CI, 1.09 to 3.75; P=0.02) and was reduced in nondiabetic patients during the first 6 months of olmesartan use (HR, 0.72; 95% CI, 0.55 to 0.96; P=0.02), and with use of 6 months or longer (HR, 0.46; 95% CI, 0.24 to 0.86; P=0.01). Secondary: Not reported
Diabetes/Diabetic Nephropathy/Renal Disease				
White et al.[43] (2016) Azilsartan medoxomil 40 or 80 mg vs olmesartan 40 mg vs	Pooled analysis of 3 DB, PC or AC, RCTs Patients with impaired fasting glucose (prediabetes mellitus) and T2DM	N=3821 6 to 8 weeks	Primary: Changes from baseline in both 24-h and clinic SBP Secondary: Safety and tolerability	Primary: Baseline 24-h mean SBPs were approximately 145 and 146 mmHg in the prediabetes mellitus and T2DM subgroups, respectively; corresponding clinic SBPs were approximately 158 and 159 mmHg. Baseline HbA1c values for each subgroup were normoglycemic, 5.3%; prediabetes mellitus, 6.0%; and T2DM, 6.9%. Changes from baseline in 24-h or clinic SBP were significantly greater with azilsartan, 80 mg compared with either olmesartan 40 mg or valsartan 320 mg in all subgroups in each pool. Secondary: Safety and tolerability were similar among the active treatment and placebo subgroups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
valsartan 320 mg				
Mogensen et al.[44] (2000) CALM Lisinopril 20 mg QD vs candesartan 16 mg QD vs lisinopril 20 mg QD plus candesartan 16 mg QD Patients received 12 weeks monotherapy followed by an additional 12 weeks of monotherapy or combination therapy.	DB, DD, MC, PG, RCT Patients 30 to 75 years old with HTN, type 2 diabetes, and microalbuminuria	N=199 24 weeks	Primary: Blood pressure and urinary albumin:creatinine ratio Secondary: Not reported	Primary: At 12 weeks, mean reductions in DBP were 9.7 mm Hg (P<0.001) and 9.5 mm Hg (P<0.001), respectively, and in urinary albumin:creatinine ratio were 46% (P<0.001) and 30% (P<0.001) for lisinopril and candesartan, respectively. Compared to either agent alone, at 24 weeks the combination of lisinopril plus candesartan resulted in 16.3 mm Hg reduction in mean DBP vs 10.4 mm Hg for candesartan alone (P<0.001) and 10.7 mm Hg for lisinopril alone (P<0.001). The reduction in urinary albumin:creatinine ratio with combination treatment (50%) was greater than with lisinopril alone (39%; P<0.001) and candesartan alone (24%; P=0.05). All treatments were generally well tolerated. Secondary: Not reported
Lewis et al.[45] (2001) IDNT Irbesartan 300 mg/day	DB, MC, PC, PRO, RCT Patients 30 to 70 years old, with type 2 diabetes mellitus, HTN, and	N=1,715 2.6 years	Primary: Composite of risk of doubling serum creatinine, ESRD, or death from any cause	Primary: Compared to placebo, irbesartan 300 mg/day resulted in a 20% lower relative risk of the composite primary outcome (P=0.02). Irbesartan treatment was associated with a 33% lower risk of doubling serum creatinine (P=0.003) and 23% trend towards lower risk of ESRD (P=0.07) compared to placebo. There was no significant difference in risk of death from any cause for irbesartan compared to placebo (P=0.57).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs amlodipine 10 mg/day vs placebo	nephropathy		Secondary: Composite of death from cardiovascular causes, nonfatal MI, heart failure requiring hospitalization, permanent neurologic deficit caused by a cerebrovascular event, or lower limb amputation	Compared to amlodipine, irbesartan treatment resulted in a 23% lower risk of composite primary outcome (P=0.006). Irbesartan treatment was associated with a 37% lower risk of doubling serum creatinine vs amlodipine (P<0.001) and 23% trend towards lower risk of ESRD vs amlodipine (P=0.07). There was no significant difference in risk of death from any cause (P=0.80). Secondary: There were no significant differences in the secondary cardiovascular composite end point (P=0.40 and P=0.79 for irbesartan vs placebo and amlodipine, respectively).
Parving et al.[46] (2001) IRMA2 Irbesartan 150 or 300 mg/day vs placebo	DB, MC, PC, RCT Patients with HTN, type 2 diabetes mellitus and microalbuminuria	N=590 2 years	Primary: Time to onset of diabetic nephropathy Secondary: Changes in level of albuminuria and creatinine clearance and restoration of normoalbuminuria	Primary: The primary end point was reached in 5.2% of patients in the irbesartan 300 mg group (P<0.001) and 9.7% of patients in the irbesartan 150 mg group (P=0.08) compared to 14.9% of patients receiving placebo. Secondary: Irbesartan reduced the level of urinary albumin excretion by 38% in patients receiving the 300 mg dose and 24% in patients receiving the 150 mg dose vs 2% for placebo (P<0.001 for the combined irbesartan groups vs placebo and P<0.001 for the 300 vs 150 mg doses). There was no significant difference in the decline in creatinine clearance among the 3 groups. Restoration of normoalbuminuria was observed in 34% of patients receiving irbesartan 300 mg (P=0.006), 24% of patients receiving irbesartan 150 mg and 21% with placebo.
Persson et al.[47] (2009) Irbesartan 300 mg QD vs	DB, RCT, XO Adults with type 2 diabetes, HTN, and albuminuria	N=26 Four 2-month treatment periods	Primary: Albuminuria (urinary albumin excretion rate) Secondary: 24-hour blood	Primary: Treatment with aliskiren led to a significant reduction in albuminuria by 48% compared to placebo (P<0.001). Treatment with irbesartan led to a significant reduction in albuminuria by 58% compared to placebo (P<0.001). There was no significant difference in albuminuria between aliskiren and irbesartan (P value not reported). The combination of aliskiren and irbesartan significantly reduced albuminuria by 71% compared to placebo (P<0.001), which was also

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
aliskiren 300 mg QD vs aliskiren 300 mg QD and irbesartan 300 mg QD vs placebo			pressure and GFR	significantly better than with monotherapy (P<0.001 for aliskiren and P=0.028 for irbesartan). Secondary: SBP and DBP 24-hr blood pressure were reduced by 3 and 4 mm Hg, respectively by aliskiren (P value not significant and P=0.009, respectively), 12 and 5 mm Hg, respectively by irbesartan (P<0.001 and P=0.002, respectively), and 10 and 6 mm Hg, respectively with the combination (P=0.001 and P <0.001, respectively) compared to placebo. There was no significant change in 24-hr blood pressure with irbesartan compared to combination therapy. GFR was significantly reduced 4.6 mL/min/1.73 m^2 with aliskiren (P=0.037), 8.0 mL/min/1.73 m^2 with irbesartan (P<0.001), and 11.7 mL/min/1.73 m^2 with the combination (P<0.001) compared to placebo.
Chrysostomou et al.[48] (2006) Ramipril 5 mg/day plus spironolactone 25 mg/day and placebo vs ramipril 5 mg/day plus irbesartan 150 mg/day and placebo vs ramipril 5 mg/day plus placebo and placebo	DB, PC, RCT Patients 18 to 75 years of age, with a 24 hour urinary protein excretion >1.5 g/24 hours on ≥2 occasions ≥3 months apart, serum creatinine level ≤200 µmol/L with <20% variability in the preceding 3 months and treatment with an ACE inhibitor ≥6 months	N=41 6 months	Primary: Change in 24 hour urinary protein excretion at three months Secondary: Change in 24 hour urinary protein excretion at six months, change in blood pressure and creatinine clearance, adverse effects	Primary: Compared to ramipril-treated patients, the 24 hour urinary protein excretion reduction at three months was significantly greater in ramipril plus spironolactone-treated patients (P=0.004). Ramipril-, irbesartan- and spironolactone-treated patients exhibited a significant reduction in 24 hour urinary protein excretion compared to ramipril-treated patients (P<0.001). There was no significant difference in 24 hour urinary protein excretion with ramipril- and ramipril plus irbesartan-treated patients (P=1.00). At three months, spironolactone-treated patients exhibited a significant reduction in proteinuria from baseline (P≤0.001). In contrast, non-spironolactone-treated patients did not experience a significant reduction in proteinuria from baseline (P=0.840). Secondary: At six months, spironolactone-treated patients exhibited the greatest reduction in proteinuria compared to the other treatments (P<0.05). At six months, DBP was higher among ramipril monotherapy-treated patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs spironolactone 25 mg/day plus irbesartan 150 mg/day and ramipril 5 mg/day				compared to the other treatments (P=0.046). There was no difference in SBP among the treatments (P value not reported). There were no differences in creatinine clearance among the treatments (P>0.05). Gynecomastia was not observed with any of the treatments.
Bianchi et al.[49] (2010) Ramipril 10 mg and atorvastatin 10 mg QD (conventional therapy) vs spironolactone 25 mg, ramipril 10 mg, irbesartan 300 mg, and atorvastatin 10 mg QD (intensive therapy) The addition of diuretics, calcium antagonists, β-blockers or α1-receptor antagonists were added to achieve blood pressure <130/80 mm Hg	RCT, OL Patients with a clinical diagnosis of idiopathic chronic glomerulonephritis and urine protein-creatinine ratio >1 g/g	N=128 36 months	Primary: Changes over time in proteinuria and eGFR Secondary: Adverse events, drop outs	Primary: SBP decreased more in the intensive-therapy group (from 156.6 to 113.5 mm Hg) than in the conventional therapy group (from 155.7 to 122.7 mm Hg; P<0.01). Urine protein excretion decreased from 2.65 to 0.45 g/g creatinine with intensive therapy (P<0.001). With conventional therapy, urine protein excretion decreased from 2.60 to 1.23 g/g creatinine (P<0.001). With intensive therapy, eGFR did not significantly change over time (64.6 vs 62.9 mL/min/1.73 m^2). With conventional therapy, eGFR decreased from 62.5 to 55.8 mL/min/1.73 m^2 (P<0.01). Secondary: In the conventional therapy group, eight patients discontinued the study due to hyperkalemia, cough, and rapid deterioration in kidney function. In the intensive therapy group, 15 dropped out due to hyperkalemia, cough, and hypotension. Nine patients in the intensive therapy group developed gynecomastia. Twelve patients on conventional and 31 on intensive therapy had to interrupt the study temporarily because of low blood pressure. No patient developed an increase in creatine kinase, alanine aminotransferase, and alkaline phosphatase levels during the study.
Brenner et al.[50] (2001)	DB, PC, RCT	N=1,513	Primary: Composite of risk of	Primary: Compared to placebo, losartan resulted in a 16% reduction of composite

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
RENAAL Losartan 50 to 100 mg QD vs placebo	Patients 31 to 70 years of age with HTN, type 2 diabetes mellitus and nephropathy on conventional antihypertensive therapy	3.4 years	doubling of serum creatinine, ESRD, or death from any cause Secondary: Composite of morbidity and mortality from cardiovascular causes, proteinuria, rate of progression of renal disease	primary end point (P=0.02). Losartan treatment produced a 25% reduction of doubling serum creatinine vs placebo (P=0.006) and 28% reduction in ESRD vs placebo (P=0.002). No differences in mortality were reported (P=0.88). Secondary: There was no significant difference between the losartan and placebo groups in the composite end point of morbidity and mortality from cardiovascular causes. Losartan treatment led to an average reduction in the level of proteinuria by 35% (P<0.001 vs placebo). Losartan reduced the rate of decline in renal function by 18% (P=0.01 vs placebo).
Kiernan et al.[51] (2015) HEAAL Losartan 50 mg vs losartan 150 mg	DB, MC, RCT Patients with HFrEF, NYHA functional class II to IV; LVEF ≤40%; stable cardiovascular medical therapy for at least two weeks; and known intolerance to ACEIs	N=3,843	Primary: eGFR levels, SCr, renal function and association with clinical outcomes Secondary: Not reported	Primary: Compared with 50 mg, 150 mg losartan led to a greater reduction in eGFR across time (mean difference, −3.76 ml/min/1.73 m^2; P<0.0001). This difference was driven by early changes, and differences in eGFR after four months were not significant (mean difference, 0.42 ml/min/1.73 m^2; P=0.15). Although an increase in SCr >0.3 mg/dL from baseline was associated with increased risk of death or hospitalization for HF (HR, 1.36; P<0.0001), the relationship was not significant if the change occurred before four months (HR, 1.09; P=0.20). Despite increased risk of worsening renal function, 150 mg losartan was associated with reduced risk of death or hospitalization for HF compared with 50 mg (HR, 0.85; P<0.0001). Secondary: Not reported
Hou et al.[52] (2007) ROAD Benazepril 10 mg/day vs	OL, PRO, RCT Patients aged 18 to 70 years with proteinuria and chronic renal	N=360 3.7 years (median follow-up)	Primary: Time to composite of doubling of serum creatinine, ESRD or death	Primary: Compared to the conventional dosages, optimal antiproteinuric dosages of benazepril and losartan that were achieved through up-titration were associated with a 51 and 53% reduction in the risk for the primary end point (P=0.028 and P=0.022, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
individual up-titration (10 to 40 mg/day with median dose of 20 mg/day) or losartan 50 mg/day vs individual up-titration (50 to 200 mg/day with median dose of 100 mg/day) Up-titration was performed to optimal antiproteinuric and tolerated dosages, and then these dosages were maintained.	insufficiency who did not have diabetes		Secondary: Changes in level of proteinuria, rate of progression of renal disease	There was no statistically significant difference between benazepril and losartan in the overall relative risk reduction at their respective optimal antiproteinuric dosages or at conventional dosages. Secondary: Optimal antiproteinuric dosages of benazepril and losartan at comparable blood pressure control, achieved a greater reduction in both proteinuria and the rate of decline in renal function compared to their conventional dosages. There was no significant difference in proteinuria reduction between benazepril and losartan at both conventional and optimal antiproteinuric dosages. Changes in renal function were similar between benazepril and losartan arms at both conventional and optimal antiproteinuric doses (P>0.05). There was no significant difference for the overall incidence of major adverse events between groups that were given conventional and optimal dosages in any of the treatment arms.
Fried et al.[53] (2013) VA NEPHRON-D Losartan with lisinopril vs losartan alone	DB, MA, RCT Veterans with proteinuric diabetic kidney disease, an estimated GFR of 30.0 to 89.9 ml/minute/1.73 m^2 , and a urinary albumin-to-creatinine ratio of ≥300	N=1448 Median follow-up 2.2 years	Primary: First occurrence of a decline in the eGFR (an absolute decrease of ≥30 ml/minute/1.73 m^2 if the eGFR was ≥60 ml/minute/1.73 m^2 at randomization or a relative decrease of ≥50% if the eGFR was <60 ml/minute/1.73 m^2), ESRD, or death	The trial was stopped early because the absolute risk of serious adverse events appeared to be greater than the potential benefit of reducing primary end-point events. Primary: There were 152 primary end-point events in the monotherapy group (21.0%) and 132 in the combination-therapy group (18.2%).The risk of the primary end point did not differ significantly between the two groups. Secondary: There were 101 secondary end-point events (a decline in the estimated GFR or ESRD) in the monotherapy group (14.0%) and 77 events in the combination-therapy group (10.6%).There was no significant between-group difference in mortality or ESRD (Table 2), though the number of ESRD events was small.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: First occurrence of a decline in the eGFR or ESRD Tertiary: CV events, slope of change in eGFR, and change in albuminuria at 1 year	Tertiary: There was no significant difference in the rate of cardiovascular events between the two groups. There was no significant difference in treatment effect on the decline in the estimated GFR (P=0.17). During adjustment of the losartan dose, the median urinary albumin-to-creatinine ratio declined from 959 to 807 (P=0.001). There was a further decline from randomization to 1 year, with a greater decline in the combination-therapy group (from 786 to 517) than in the monotherapy group (from 829 to 701) (P<0.001).
Nakao et al.[54] (2003) COOPERATE Trandolapril 3 mg/day vs losartan 100 mg/day vs trandolapril and losartan at equivalent doses	DB, MC, PC, RCT Patients aged 18 to 70 years with chronic nephropathy (nondiabetic renal disease)	N=263 3 years	Primary: Composite of time to doubling of serum creatinine or ESRD Secondary: Changes in blood pressure, daily urinary protein excretion, adverse effects	Primary: The combined end point was reached in 11% of patients in the combination trandolapril and losartan group compared to 23% of patients in the trandolapril (P=0.018) and 23% of patients in the losartan group (P=0.016). Secondary: Mean SBP and DBP reductions were similar among the three treatment groups (P=0.109). All patients receiving active treatment had significant decreases in urinary protein excretion, but the greatest difference was seen with the combination trandolapril and losartan group compared to trandolapril or losartan (-75.6, -44.3, and -42.1%, respectively; P=0.01). The frequency of adverse events did not differ between groups, although a slightly higher occurrence of hyperkalemia and dry cough was recorded in the trandolapril and combination groups than in the losartan group.
Mann et al.[55] (2009) TRANSCEND Telmisartan 80 mg QD vs	DB, MC, PC, RCT Adults with known cardiovascular disease or diabetes with end-organ damage but without macroalbuminuria or heart failure who	N=5927 56 months	Primary: Composite outcome: first occurrence of dialysis, renal transplant, doubling of serum creatinine, or death	Primary: The composite outcome of dialysis, doubling of serum creatinine, or death did not significantly differ between the telmisartan and placebo groups (412 patients [14.0%] vs 381 patients [12.8%]; HR, 1.10 [CI, 0.95 to 1.26]; P=0.193). The incidence of the composite outcome of dialysis or doubling of serum creatinine was similar with telmisartan and placebo (58 patients [1.96%] vs 46 patients [1.55%]; HR, 1.29 [95% CI, 0.87 to 1.89]; P=0.20).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	cannot tolerate ACE inhibitors		Secondary: Changes in the eGFR, progression of proteinuria, and individual components of the primary outcome	Secondary: Doubling of serum creatinine was more frequent with telmisartan than with placebo (56 vs 36 patients; P=0.031). Decreases in eGFR were greater with telmisartan than with placebo (mean change in eGFR, -3.2 mL /min per 1.73 m^2 [SD, 18.3] vs -0.26 mL/min per 1.73 m^2 [SD, 18.0]; P <0.001).
Foulquier et al.[56] (2014) TRANSCEND Telmisartan 80 mg QD vs placebo	Post-hoc analysis Patients in the TRANSCEND trial stratified by hypertensive and nonhypertensive	N=5927 56 months	Primary: Composite outcome: first occurrence of dialysis, renal transplant, doubling of serum creatinine, or death Secondary: Changes in the eGFR, progression of proteinuria, and individual components of the primary outcome	Primary: For the primary four-fold endpoint, No difference in the effect of treatment between hypertensive and nonhypertensive patients was found. No significant improvement with telmisartan over placebo in both hypertensive and nonhypertensive patients was seen. Secondary: New onset of LVH, evaluated by ECG, was significantly less in hypertensive and nonhypertensive patients treated with telmisartan (hypertensive patients: –36%; P=0.0002; nonhypertensive patients: –58%; P=0.027). Albuminuria increased less with telmisartan than with placebo in the hypertensive population, as the risks for new microalbuminuria and macroalbuminuria were lower than with placebo (P=0.0004 and P=0.009, respectively). In the nonhypertensive population, the risks were not modified by the treatment. However, according to the interaction tests, there is no difference in the effect of telmisartan in hypertensive and nonhypertensive patients, suggesting that telmisartan might also reduce the new onset of microalbuminuria and macroalbuminuria in nonhypertensive patients.
Barnett et al.[57] (2004) DETAIL Enalapril 20 mg/day vs telmisartan 80	DB, MC, PG, RCT Patients aged 35 to 80 years with type 2 diabetes and HTN	N=250 5 years	Primary: Change in the GFR Secondary: Annual changes in GFR, serum creatinine level, urinary albumin excretion, and blood pressure; rates of	Primary: After five years, GFR decreased by 17.9 mL/minute/1.73 m^2 with telmisartan compared to 14.9 mL/min/1.73 m^2 with enalapril (mean difference, -3.0 mL/min/1.73 m^2; 95% CI, -7.6 to 1.6). Therefore, the changes in GFR were comparable between the groups. Secondary: The effects of the two agents on the secondary end points were not significantly different after five years.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day			ESRD and cardiovascular events; all-cause mortality	
Galle et al.[58] (2008) Telmisartan 80 mg QD vs valsartan 160 mg QD Additional antihypertensive therapy was allowed.	DB, MC, PG, PRO, RCT, non-inferiority study Hypertensive patients (SBP/DBP >130/80 mm Hg) with type 2 diabetes, proteinuria and serum creatinine ≤3.0 mg/dL	N=885 12 months	Primary: Change from baseline in the 24-hour proteinuria Secondary: Changes in 24-hour albuminuria, eGFR and inflammatory parameters	Primary: Telmisartan and valsartan produced comparable reductions in 24-hour urinary protein excretion rates: geometric mean reduction was 33% for both telmisartan and valsartan. Secondary: No significant differences between treatments were seen in changes from baseline in 24-hour urinary albumin excretion rate and GFR at 12 months. With both treatments, greater renoprotection was seen among patients with better blood pressure control. No significant changes in C-reactive protein were noted for either group at 12 months.
Fogari et al.[59] (2007) Telmisartan and amlodipine 40 to 160-2.5 QD (fixed-dose combination) vs telmisartan and amlodipine 40-2.5 mg QD (fixed-dose combination)	DB, MC, RCT Patients 35 to 70 years of age with essential HTN, type 2 diabetes mellitus and microalbuminuria (UAER >30 and <300 mg/24 hr)	N=210 64 weeks	Primary: Blood pressure, UAER, creatinine clearance, plasma potassium, fasting glycemia, and HbA_{1c} Secondary: Not reported	Primary: High-dose telmisartan/low-dose amlodipine and low-dose telmisartan/high-dose amlodipine combination produced a similar reduction in SBP and DBP with no significant difference between the two regimens at any time of the study. With increasing doses of telmisartan (40, 80, 120, and 160 mg), SBP and DBP values were reduced from baseline by 16 and 10 mm Hg, respectively (P<0.01), 24 and 21 mm Hg, respectively (P<0.001), 23 and 21 mm Hg, respectively (P<0.001), and 24 and 21 mm Hg, respectively (P<0.001). With increasing dose of amlodipine (2.5, 5, 7.5, and 10 mg) SBP and DBP values were reduced from baseline by 16 and 10 mm Hg, respectively (P<0.01), 25 and 22 mm Hg, respectively (P<0.001), 25 and 21 mm Hg, respectively (P<0.001), and 25 and 22 mm Hg, respectively (P<0.001). Reductions of UAER from baseline were of 34.6 mg/24 hr (P<0.05 vs baseline), 62.9 mg/24 hr (P<0.01 vs baseline and P<0.05 vs A group), 86.5

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				mg/24 hr (P<0.001 vs baseline and P<0.01 vs A group) and 102 mg/24 hr (P<0.0001 vs baseline and P<0.001 vs A group) for telmisartan 40, 80, 120, and 160 mg/amlodipine 2.5 mg daily, respectively. Reductions of UAER from baseline were of 35.1 mg/24 hr (P<0.05 vs baseline), 46.2 mg/24 hr (P<0.03 vs baseline), 50.3 mg/24 hr (P<0.03 vs baseline), and 45 mg/24 hr (P<0.03 vs baseline) for amlodipine-telmisartan 2.5-40, 5-40, 7.5-40, and 10-40 mg/day, respectively. Creatinine clearance did not significantly change with either treatment. Neither combination affected levels of plasma potassium or fasting glucose. The HbA_{1c} levels were not significantly influenced by either treatment.
Viberti et al.[60] (2002) MARVAL Valsartan 80 mg QD vs amlodipine 5 mg QD A target blood pressure of 135/85 mm Hg was aimed for by dose-doubling followed by the addition of bendrofluazide* and doxazosin whenever needed.	AC, DB, RCT Patients 35-75 years old with type 2 diabetes mellitus and microalbuminuria, with or without HTN	N=332 24 weeks	Primary: Change in UAER; proportion of patients who returned to normal albuminuria Secondary: Proportion of patients returning to normoalbuminuria	Primary: Valsartan resulted in a UAER reduction of 44% at 24 weeks compared to baseline vs an 8% reduction with amlodipine (P<0.001). Valsartan lowered UAER similarly in both the hypertensive and normotensive groups. Over the study period, blood pressure reductions were similar between the two treatments and at no time point was there a between-group significant difference in blood pressure values in either the hypertensive or the normotensive subgroup. Secondary: The proportion of patients returning to normal albuminuria was greater with valsartan (29.9%) vs amlodipine (14.5%; P=0.001).
Casas et al.[61] (2005) ACE inhibitor or	MA (127 trials) Studies in adults that examined the effect	N=not reported 4.2 years	Primary: Doubling of serum creatinine, and ESRD	Primary: Treatment with ACE inhibitors or ARBs resulted in a nonsignificant reduction in the risk of doubling of creatinine vs other antihypertensives (P=0.07) with no differences in the degree of change of SBP or DBP between the groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ARBs compared to placebo vs ACE inhibitor or ARBs compared to other antihypertensive drugs (β-adrenergic blocking agents, α-adrenergic blocking agents, calcium-channel blocking agents, or combinations) Specific agents and doses were not specified.	of any drug treatment with a blood pressure lowering action on progression of renal disease	(mean)	Secondary: Serum creatinine, urine albumin excretion and GFR	A small reduction in ESRD was observed in patients receiving ACE inhibitors or ARBs compared to other antihypertensives (P=0.04) with no differences in the degree of change of SBP or DBP between the groups. Secondary: Small reductions in serum creatinine and in SBP were noted when ACE inhibitors or ARBs were compared to other antihypertensives (P=0.01). Small reduction in daily urinary albumin excretion in favor of ACE inhibitor or ARBs were reported when these agents were compared to other antihypertensives (P=0.001). Compared to other drugs, ACE inhibitors or ARBs had no effect on the GFR.
Strippoli et al.[62] (2004) ACE inhibitors vs placebo or ARBs vs placebo	MA Patients with diabetic nephropathy	43 trials ≥6 months (range 6 to 63.6 months)	Primary: All-cause mortality, renal outcomes (ESRD, doubling of serum creatinine, microalbuminuria to macroalbuminuria) Secondary: Not reported	Primary: ACE inhibitors significantly reduced all-cause mortality compared to placebo or no treatment (RR, 0.79; 95% CI, 0.63 to 0.99; P=0.04). There was a nonsignificant trend for reduction in ESRD (P=0.07) and doubling of serum creatinine (P=0.08) with ACE inhibitors compared to placebo or no treatment. ACE inhibitors significantly reduced the risk of progression from microalbuminuria to macroalbuminuria (P=0.0007) and increased regression back to normoalbuminuria (P<0.0001) compared to placebo or no treatment. ARBs did not significantly reduce all-cause mortality compared to placebo or no treatment (RR, 0.99; 95% CI, 0.85 to 1.17; P=0.95). ARBs significantly reduced the risk of ESRD (P=0.001) and doubling of serum creatinine (P=0.004). ARBs significantly decreased the risk of progression to macroalbuminuria (P=0.001) and increased regression to normoalbuminuria (P=0.02) compared to placebo or no treatment.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
or ACE inhibitors vs ARBs				The three trials that compared ACE inhibitors to ARBs did not report on all-cause mortality, ESRD or doubling of serum creatinine. Progression from microalbuminuria to macroalbuminuria was reported in one trial (N=92) and there was no significant difference in risk, with the point estimate favoring ACE inhibitors (RR, 0.16; 95% CI, 0.02 to 1.44). Regression from microalbuminuria to normoalbuminuria in 1 trial showed a nonsignificant difference in the risk. Secondary: Not reported
Strippoli et al.[63] (2006) ACE inhibitors vs placebo or ARBs vs placebo or ACE inhibitors vs ARBs	MA Patients with diabetic kidney disease	N=12,067 (49 trials) ≥6 months	Primary: All-cause mortality, ESRD, doubling of serum creatinine concentration, progression from micro- to macroalbuminuria, regression from micro- to normoalbuminuria, drug-related toxicity (including cough, headache, hyperkalemia, impotence and pedal edema) Secondary: Not reported	Primary: There was no significant difference in the risk of all-cause mortality for ACE inhibitors vs placebo or no treatment (RR, 0.91; 95% CI, 0.71 to 1.17) and ARBs vs placebo or no treatment (RR, 0.99; 95% CI, 0.85 to 1.17). No statistically significant reduction in the risk of all-cause mortality was found in the three studies that compared ACE inhibitors with ARBs (RR, 0.92; 95% CI, 0.31 to 2.78). A subgroup analysis of studies showed a significant reduction in the risk of all-cause mortality with the use of full-dose ACE inhibitors (RR, 0.78; 95% CI, 0.61 to 0.98) but not when using half or less than half the maximum tolerable dose of ACE inhibitors (RR, 1.18; 95% CI, 0.41 to 3.44). There was a significant reduction in the risk of ESRD with ACE inhibitors and ARBS compared to placebo or no treatment (RR, 0.60; 95% CI, 0.39 to 0.93 and RR, 0.78; 95% CI, 0.67 to 0.91, respectively). There was a significant reduction in the risk of doubling of serum creatinine concentration with ACE inhibitors and ARBS (RR, 0.68; 95% CI, 0.47 to 10 and RR, 0.79; 95% CI, 0.67 to 0.93, respectively). ACE inhibitors and ARBS significantly reduced the risk of progression from micro- to macroalbuminuria (RR, 0.45; 95% CI, 0.29 to 0.69 and RR, 0.49; 95% CI, 0.32 to 0.75, respectively). ACE inhibitors and ARBS significantly increased the regression from micro- to normoalbuminuria compared to placebo or no treatment (RR, 3.06; 95% CI, 1.76 to 5.35 and RR, 1.42; 95% CI, 15 to 1.93, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The seven studies that compared ACE inhibitors to ARBS did not report the outcome of ESRD or doubling of serum creatinine. Progression from micro- to macroalbuminuria and from micro- to normoalbuminuria were evaluated each in one trial and showed a nonsignificant difference in the risk between ACE inhibitors and ARBS. ACE inhibitors were associated with a significant increase in the risk of cough but not hyperkalemia, headache or impotence when compared to placebo or no treatment. ARBS were associated with a significant increase in the risk of hyperkalemia but not cough or headache compared to placebo or no treatment. Secondary: Not reported
Heart Failure				
Cohn et al.[64] (2001) Val-HeFT Valsartan 160 mg BID vs placebo	DB, PC, RCT Patients ≥18 years old with a cardiovascular history and NYHA II to IV heart failure	N=5,010 2 years	Primary: Mortality and composite end point of morbidity and mortality Secondary: Change in NYHA class, ejection fraction, signs and symptoms of heart failure, QOL	Primary: Compared to placebo, valsartan resulted in no significant differences in all-cause mortality. Patients treated with valsartan experienced a 13% decrease in the composite end point (P=0.009) and 27% decrease in heart failure hospitalizations (P<0.001). Secondary: Treatment with valsartan resulted in significant improvements in NYHA class, ejection fraction, signs and symptoms of heart failure and QOL as compared to placebo (P<0.01). In a post hoc analysis of the combined end point and mortality in subgroups defined according to baseline treatments with ACE inhibitors or β-blockers, valsartan had a favorable effect in patients receiving neither or one of these types of drugs but an adverse effect in patients receiving both types of drugs.
Pfeffer et al.[65] (2003) CHARM Overall Programme Candesartan 32	DB, PC, PG, RCT Summary of all CHARM sub-studies	N=7,599 37.7 months	Primary: All-cause mortality (Overall Programme) and cardiovascular death or hospital	Primary: In the overall analysis, candesartan 32 mg daily resulted in an 18% decreased risk of all-cause mortality compared to placebo (23 vs 25%; unadjusted HR, 0.91; 95% CI, 0.83 to 10; P=0.055; covariate adjusted HR, 0.90; 95% CI, 0.82 to 0.99; P=0.032).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day (±ACE inhibitor) vs placebo (±ACE inhibitor)			admission for CHF (all of the component trials) Secondary: Not reported	Annual mortality rates were 8.1 and 8.8% for patients treated with candesartan and placebo, respectively. The lower mortality in patients treated with candesartan vs placebo was attributed to fewer cardiovascular deaths (18 vs 20%; unadjusted HR, 0.88; 95% CI, 0.79 to 0.97; P=0.012). Hospital admissions for CHF were significantly fewer in patients treated with candesartan than placebo (20 vs 24%; P<0.0001). Secondary: Not reported
McMurray et al.[66] (2003) CHARM-Added Candesartan 32 mg/day in patients already taking ACE inhibitors vs placebo in patients already taking ACE inhibitors	DB, MC, PC, RCT Patients ≥18 years old with LVEF ≤40%, NYHA II to IV heart failure and treatment with an ACE inhibitor at a constant dose for 30 days or longer	N=2,548 41 months	Primary: Composite of cardiovascular death and hospitalization for heart failure Secondary: Composites of primary end point and MI, nonfatal stroke and coronary revascularization	Primary: Compared to placebo, candesartan 32 mg/day when added to ACE inhibitors resulted in a 15% reduction in the primary end point (P=0.011), 16% decrease in cardiovascular deaths (P=0.029) and 17% reduction in heart failure hospitalizations (P=0.014). Secondary: Fewer patients experienced cardiovascular death, hospital admission for CHF, MI, stroke, or coronary revascularization in the candesartan group (42.9%) compared to placebo (46.9%; P=0.015).
Granger et al.[67] (2003) CHARM-Alternative Candesartan 32 mg/day vs placebo	DB, PC, RCT Patients ≥18 years old with LVEF ≤40%, NYHA II to IV heart failure and intolerance to ACE inhibitors	N=2,028 33.7 months	Primary: Composite of cardiovascular death and hospitalization for heart failure Secondary: Composites of primary end point and MI, nonfatal stroke and coronary	Primary: Compared to placebo, candesartan 32 mg/day resulted in a 30% reduction of the composite end point (P<0.0001). A 20% decrease in cardiovascular death (P=0.02) and 39% reduction in heart failure hospitalizations (P<0.0001) were noted in patients treated with candesartan compared to placebo. Study drug discontinuation rates were similar in the candesartan (30%) and placebo (29%) groups.

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			revascularization	Secondary: Fewer patients experienced cardiovascular death, hospital admission for CHF, MI, stroke, or coronary revascularization in the candesartan group (39.1%) compared to placebo (44.9%; P<0.0001).
Yusuf et al.[68] (2003) CHARM-Preserved Candesartan 32 mg/day vs placebo	DB, PC, RCT Patients ≥18 years old with preserved ejection fraction (>40%) and symptomatic heart failure	N=3,025 36.6 months	Primary: Composite of cardiovascular death and hospitalization for heart failure Secondary: Composites of primary end point and MI, nonfatal stroke and coronary revascularization	Primary: Compared to placebo, candesartan 32 mg/day resulted in an insignificant 14% trend towards lower incidence of the primary end point (P=0.051). Candesartan significantly reduced the risk of heart failure hospitalization (16%; P=0.047) but did not significantly decrease the risk of cardiovascular death (P=0.635). Secondary: The composite of cardiovascular death, hospitalization for CHF, MI, and stroke was significantly lower in the candesartan group compared to placebo (25.6 vs 28.4%; P=0.037). There was no significant difference in the composite of cardiovascular death, hospital admission for CHF, MI, stroke, or coronary revascularization in the candesartan group (30.4%) compared to placebo (32.9%; P=0.130).
Castagno et al.[69] (2012) CHARM Candesartan 32 mg/day (±ACE inhibitor) vs placebo (±ACE inhibitor)	Subgroup analysis according to baseline heart rate and LVEF Patients with chronic heart failure	N=7,597 Duration varied	Primary: Composite of cardiovascular death or heart failure hospital stay Secondary: Not reported	Primary: Patients with the highest heart rate tertile had worse outcomes when compared to patients in the lowest heart rate group (HR, 1.23; 95% CI, 1.11 to 1.36; P<0.001). The relationship between heart rate and outcomes was similar across LVEF categories, and was not influenced by use of β-blockers (P>0.10 for both endpoints). Secondary: Not reported
Pitt et al.[70] (1997) ELITE Captopril 50 mg	DB, MC, PG, RCT Patients ≥65 years with symptomatic heart failure (NYHA	N=722 1 year	Primary: Change in renal function Secondary:	Primary: No difference between losartan and captopril was reported in the rate of persistent rise in serum creatinine concentrations (10.5% for both groups). Secondary:

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TID vs losartan 50 mg QD	class II to IV and LVEF ≤40%), and no history of prior ACE inhibitor therapy		Composite of death and/or hospital admission for heart failure, all-cause mortality, admission for heart failure, NYHA class, admission for MI or unstable angina	Death and/or hospital admission for heart failure was recorded in 9.4% of patients receiving losartan and 13.2% for patients receiving captopril (risk reduction, 32%; 95% CI, -4 to 55; P=0.075). This risk reduction was primarily due to a decrease in all-cause mortality (4.8 vs 8.7%; risk reduction, 46%; 95% CI, 5 to 69; P=0.035). Admissions with heart failure were the same in both groups (5.7%), as was improvement in NYHA functional class from baseline. Admission to hospital for any reason was less frequent with losartan than with captopril treatment (22.2 vs 29.7%; P=0.014). More patients discontinued therapy due to adverse events with captopril (20.8%) than losartan (12.2%; P=0.002).
Pitt et al.[71] (2000) ELITE II Captopril 50 mg TID vs losartan 50 mg QD	DB, MC, PG, RCT Patients ≥60 years old with symptomatic heart failure (NYHA II to IV and LVEF ≤40%), and no history of prior ACE inhibitor therapy	N=3,152 555 days (mean follow-up)	Primary: All-cause mortality Secondary: Composite of sudden cardiac death or resuscitated cardiac arrest	Primary: No significant difference in all-cause mortality was reported between losartan (17.7%) and captopril (15.9%; HR, 1.13; 95% CI, 0.95 to 1.35; P=0.16). Secondary: Sudden death or resuscitated cardiac arrest was observed in 9.0% of patients receiving losartan and 7.3% of patients receiving captopril (HR, 1.25; 95% CI, 0.98 to 1.60; P=0.08). Significantly fewer patients in the losartan group (excluding those who died) discontinued study treatment because of adverse events (9.7 vs 14.7%; P<0.001), including cough (0.3 vs 2.7%). Note: ELITE II trial was a larger follow-up trial to the ELITE I trial to confirm the secondary end point from the ELITE I trial, which reported a greater reduction in all-cause mortality with losartan compared to captopril.
McKelvie et al.[72] (1999) RESOLVD Enalapril 10 mg BID vs	DB, MC, PG, RCT Patients with CHF (NYHA classes II to IV), a 6 minute walk distance of 500 meters or less, and an ejection fraction	N=768 43 weeks	Primary: Change in 6-minute walk distance Secondary: Change in NYHA functional class, QOL, ejection	Primary: There were no significant differences among the groups with regards to the 6-minute walk distance over the 43 week study period. Secondary: There were no significant differences among the groups with regards to the NYHA functional class or QOL at 18 or 43 weeks.

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candesartan 4 to 16 mg QD vs candesartan 4 to 8 mg QD and enalapril 10 mg BID	<40%		fraction, ventricular volumes, neurohormone levels, safety	Ejection fraction increased more with candesartan plus enalapril than monotherapy with either agent; however, the difference was not statistically significant (P value not significant). End-diastolic volumes (P<0.01) and end-systolic volumes (P<0.05) increased less with combination therapy than with monotherapy with either agent. Aldosterone decreased with combination therapy at 17 but not 43 weeks compared to candesartan or enalapril (P<0.05). Brain natriuretic peptide decreased with combination therapy compared to candesartan and enalapril alone (P<0.01). Blood pressure decreased with combination therapy compared to candesartan or enalapril alone (P<0.05). Compared to enalapril, potassium decreased with candesartan use (P<0.05) and increased with candesartan plus enalapril (P<0.05). The proportion of patients with potassium levels ≥5.5 mmol/L was not significantly different among the treatment groups. There were no significant differences in creatinine, mortality, or hospitalizations for CHF or any cause among the three groups.
Lee et al.[73] (2004) ARBs vs placebo (±ACE inhibitor) vs ACE inhibitor monotherapy	MA Patients with chronic heart failure and high-risk acute MI	N=38,080 Duration varied	Primary: All-cause mortality and heart failure hospitalizations Secondary: Not reported	Primary: ARBs were associated with reduced all-cause mortality (OR, 0.83) and heart failure hospitalizations (OR, 0.64) vs placebo. There was no difference in all-cause mortality (OR, 1.06) and heart failure hospitalization (OR, 0.95) between ARBs and ACE inhibitors. When ARBs were combined with ACE inhibitors, all-cause mortality was not reduced (OR, 0.97) but heart failure hospitalizations were reduced (OR, 0.77) compared to treatment with ACE inhibitors alone. Two RCT comparing ARBs with ACE inhibitors in patients with high-risk acute MI did not reveal differences in all-cause mortality or heart failure hospitalization. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Hypertension				
Rakugi et al.[74] (2012) Azilsartan 20 to 40 mg QD vs candesartan 8 to 12 mg QD	DB, MC, RCT Japanese patients with grade I or II essential HTN	N=622 16 weeks	Primary: Change in baseline mean sitting DBP at week 16 Secondary: Change in baseline mean sitting SBP at week 16	Primary: After 16 weeks, the mean baseline change in sitting DBP was -12.4 and -9.8 mm Hg with azilsartan and candesartan (difference, -2.6; 95% CI, -4.08 to -1.22; P=0.0003). Secondary: After 16 weeks, the mean baseline change in sitting SBP was -21.8 and -17.5 mm Hg with azilsartan and candesartan (difference, -4.4 mm Hg; 95% CI, -6.53 to -2.20; P<0.0001).
Sica et al.[75] (2001) Azilsartan 40 or 80 mg QD vs valsartan 320 mg QD	DB, MC, RCT Patients with primary HTN	N=984 24 weeks	Primary: Change in baseline 24 hour mean ambulatory and clinic SBP Secondary: Change in baseline 24 hour mean ambulatory and clinic DBP	Primary: Azilsartan 40 and 80 mg/day significantly lowered 24 hour mean ambulatory systolic blood pressure (-14.9 and -15.3 mm Hg) compared to valsartan 320 mg/day (-11.3 mm Hg; P<0.001). Clinic SBP reductions were consistent with ambulatory blood pressure results. (-14.9 and -16.9 vs -11.6 mm Hg; P=0.015 and P<0.001). Secondary: Reductions in 24 hour mean and clinic DBP were significantly greater with azilsartan compared to valsartan (P≤0.001 for all comparisons).
Cushman et al.[76] (2012) Azilsartan and chlorthalidone 40-25 or 80-25 mg QD (fixed-dose combination product) vs olmesartan and HCTZ 40-25 mg QD (fixed-dose	DB, RCT Patients with clinic SBP 160 to 190 mm Hg and DBP ≤119 mm Hg	N=1,071 12 weeks	Primary: Change in baseline clinical SBP Secondary: Change in baseline ambulatory SBP, safety	Primary: Changes in clinic SBP were significantly greater with azilsartan and chlorthalidone (-42.5±0.8 and -44.0±0.8 mm Hg) compared to olmesartan and HCTZ (-37.1±0.8 mm Hg; P<0.0001). Secondary: Changes in ambulatory SBP were significantly greater with azilsartan and chlorthalidone (-33.9±0.8 and -36.3±0.8 mm Hg) compared to olmesartan and HCTZ (-27.5±0.8 mm Hg; P<0.0001). Adverse events leading to discontinuation of study medications were 7.9, 14.5, and 7.1% of patients receiving azilsartan and chlorthalidone 40-25 mg/day, azilsartan and chlorthalidone 80-25 mg/day, and olmesartan and HCTZ.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
combination product)				
Bönner et al.[77] (2013) Azilsartan (AZL) 20mg titrated to 40 mg vs azilsartan (AZL) 20mg titrated to 80 mg vs ramipril (RAM) 2.5 mg titrated to 10 mg	DB, RCT Patients ≥18 years of age with clinic systolic blood pressure (SBP) 150 to 180 mm Hg	N=884 24 weeks	Primary: Change in trough, seated clinic SBP Secondary: Change from baseline to week 24 in trough, seated clinic DBP, measures of ambulatory BP, and BP response rates	Primary: After 24 weeks of treatment, trough, sitting, clinic SBP decreased significantly in all the groups. The changes from baseline were significantly greater for the AZL 40 and 80 mg treatment groups (−20.6±0.95 and −21.2±0.95 mm Hg, respectively) than for RAM 10 mg (−12.2±0.95 mm Hg). The differences between the AZL-treated subjects and the RAM-treated subjects were −8.4 mm Hg for AZL 40 and −9.0 mm Hg for AZL 80 (P<0.001 for both comparisons). Secondary: Change in trough, sitting, DBP was −10.2±0.55 mm Hg in the AZL 40 mg group, −10.5±0.55 mm Hg in the AZL 80 mg and −4.9±0.56 mm Hg in the RAM 10 mg group. AZL 40 and 80 mg reduced ambulatory SBP and DBP significantly more than RAM for all ABPM time intervals evaluated, including 24-hour mean, mean daytime, mean nighttime and mean trough pressure. The differences between the AZL and RAM groups proportion of subjects achieving SBP and DBP response criteria were highly significant (P<0.001). More subjects achieved a reduction in clinic BP to <140/90 mm Hg and/or a reduction in BP≥20/10 mm Hg at week 24 following treatment with AZL compared with RAM (54.0% and 53.6% for AZL 40 and 80 mg vs 33.8% with RAM 10 mg, respectively; P<0.001).
Handley et al.[78] (2016) All subjects initiated treatment with azilsartan 40 mg QD on day one, which was added to existing treatments (a maximum of two	MC, OL, cohort Patients >18 years of age with essential HTN	N=669 56 weeks	Primary: Safety and tolerability Secondary: Efficacy	Primary: Approximately 76% of subjects overall in the two cohorts experienced an adverse event. Within each cohort, more events were reported among subjects who received add-on therapy with chlorthalidone or HCTZ. The most commonly reported adverse events (≥5% of subjects) in both cohorts combined, regardless of add-on diuretic therapy, were dizziness (14.3%), headache (9.9%), fatigue (7.2%), upper respiratory tract infection (6.7%) and urinary tract infection (5.7%). Transient serum creatinine elevations were more frequent with add-on chlorthalidone. Secondary:

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other antihypertensive agents), if applicable; at week four, azilsartan was force-titrated to 80 mg QD, if tolerated In Cohort 1, chlorthalidone 25 mg QD was the initial add-on agent for subjects who did not achieve target BP on azilsartan alone, In Cohort 2, HCTZ 12.5 mg QD was the initial add-on agent				By week 56 in Cohort 1, the overall change from baseline in clinic SBP (observed cases) was −25.2 ± 18.1 mmHg (n = 259; 21.1 ± 15.2 mmHg for subjects receiving azilsartan alone [n = 93] and −27.4 ± 19.2 mmHg for those requiring add-on chlorthalidone [n = 166]). In Cohort 2, the overall change from baseline in clinic SBP was −24.2 ± 16.0 mmHg (n = 201; −21.6 ± 14.2 for mmHg azilsartan alone [n = 68] and −25.6 ± 16.7 mmHg for add-on HCTZ [n = 133]). By week 56 in Cohort 1, the overall change from baseline in clinic DBP (observed cases) was −18.4 ± 9.5 mmHg (−18.0 ± 8.8 mmHg for azilsartan alone and −18.6 ± 9.9 mmHg with add-on CLD). By week 56 in Cohort 2, the change from baseline in clinic DBP was −17.9 ± 10.9 mmHg (−17.9 ± 9.4 mmHg for subjects azilsartan alone and −18.0 ± 11.6 mmHg with add-on HCTZ).
Kipnes et al.[79] (2015) For the 26-week, OL phase, patients received an initial dose of azilsartan 40 mg QD. At week four, the dose was force-titrated to 80 mg QD, and from week eight to week 22, chlorthalidone 25 mg QD could be added to	7-day screening phase; 26-week OL phase; 6-week randomized, DB, reversal phase; and a 7-day post-treatment AE follow-up phase Patients>18 years of age with essential HTN	26 weeks OL (N=418) followed by 6 weeks DB (N=299)	Primary: Change in trough clinic sitting DBP measured during the DB reversal phase Secondary: Change in trough clinic sitting SBP during the DB reversal phase; safety and tolerability	Primary: At the DB phase baseline (week 26), the mean clinic DBP was similar in the azilsartan and placebo groups (83.5 mm Hg and 82.3 mm Hg, respectively). This DBP level was maintained to the final visit (week 32) in patients who received azilsartan. In contrast, DBP increased among patients who received placebo, demonstrating a loss of efficacy after discontinuation of azilsartan. The least-squares mean difference between azilsartan and placebo was −7.8 mm Hg (95% CI, −9.8 to −5.8; P<0.001) at final visit. Secondary: At the DB phase baseline (week 26), the mean clinic SBP was also similar in the azilsartan and placebo groups (129.8 mm Hg and 128.2 mm Hg, respectively). As with DBP, this SBP level was maintained from week 26 to week 32 in patients who received azilsartan, whereas it increased in patients receiving placebo. The least-squares mean difference between azilsartan and placebo was −12.4 mm Hg (95% CI, −15.5 to −9.3; P<0.001) at final visit, and

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achieve target BP At week 26 (end of OL phase), patients were randomized into a 6-week, DB reversal phase in which they continued to receive azilsartan at their final dose level or were switched to placebo				the LS mean difference was statistically significant at each scheduled double-blind dosing visit. During the OL phase, approximately half (54.1%) of patients overall experienced an adverse event and these were predominantly (>90%) mild to moderate in severity. The most commonly reported adverse events overall were dizziness (8.9%) and headache (7.2%).
Neutel et al.[80] (2017) Azilsartan-chlorthalidone 20 40/12.5 mg once daily titrated to 80/25 mg if needed vs olmesartan-HCTZ 20/12.5 mg FDC once daily titrated to 40/25 mg if needed	MC, OL, RCT Patients with hypertension ≥18 years of age with clinic SBP 160 to 190 mmHg and DBP 119 mmHg or less	N=837 52 weeks	Primary: Percentage of patients with one or more treatment-emergent adverse event Secondary: Clinical laboratory tests, vital sings, BP	Primary: The percentage of patients who reported one or more treatment-emergent adverse event was 78.5% in the azilsartan-chlorthalidone group and 76.4% in the olmesartan-HCTZ group. The most commonly reported adverse events (azilsartan-chlorthalidone vs olmesartan-HCTZ) were dizziness (16.3% vs 12.6%), blood creatinine increase (21.5% vs 8.6%), headache (7.4% vs 11.0%), and nasopharyngitis (12.2% vs 11.5%). Events of hypokalemia were uncommon in both treatment groups (1.0% vs 0.7%). Secondary: Mean changes in SBP from baseline to the final visit (last observation carried forward) were −42.3±14.2 mm Hg (azilsartan-chlorthalidone) vs −38.0±14.1 mm Hg (olmesartan-HCTZ), and mean changes in DBP were −18.4±9.0 mm Hg (azilsartan-chlorthalidone) vs −15.6±9.8 mm Hg (olmesartan-HCTZ), respectively. No clinically relevant differences in urinalysis parameters, electrocardiographic parameters, or vital signs (including heart rate, body weight, or orthostatic BP) were observed between azilsartan-chlorthalidone and olmesartan-HCTZ.
Cushman et al.[81] (2018) Azilsartan-	DB, RCT Patients with primary	N=1,085 8 weeks	Primary: Change from baseline in clinic SBP	Primary: Greater reductions in clinic SBP from a baseline of 165 mmHg were observed (P<0.001) in both azilsartan-chlorthalidone arms (-37.6 and -38.2 mmHg) versus olmesartan-HCTZ (-31.5 mmHg), despite greater dose titration in the

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chlorthalidone 20/12.5 mg once daily titrated to 40/25 mg if needed or 40/12.5 mg once daily titrated to 80/25 mg if needed vs olmesartan-HCTZ 20/12.5 mg FDC once daily titrated to 40/25 mg if needed	hypertension ≥18 years of age with clinic SBP 160 to 190 mmHg and DBP 119 mmHg or less		Secondary: Changes in clinic DBP, changes in ambulatory BP monitoring parameters, proportion of patients achieving BP target	olmesartan-HCTZ group. Secondary: Greater reductions in clinic DBP in both azilsartan-chlorthalidone arms (-16.1 and -16.5 mmHg; P<0.001 vs olmesartan-HCTZ for both) versus olmesartan-HCTZ (-12.8 mmHg). At eight weeks, both azilsartan-chlorthalidone doses reduced 24-hour SBP more than olmesartan-HCTZ (-26.4 and -27.9 versus -20.7 mmHg; both P<0.001), and higher proportions in both azilsartan-chlorthalidone groups achieved target BP compared with the olmesartan-HCTZ group (69.4 and 68.9 versus 54.7%, both P<0.001). Adverse events leading to drug discontinuation occurred in 6.2, 9.5, and 3.1% with the azilsartan-chlorthalidone lower and higher doses, and olmesartan-HCTZ, respectively.
Lithell et al.[82] (2003) SCOPE Candesartan 16 mg/day vs placebo Patients also received conventional therapy with diuretics, ACE inhibitors, β-blockers, and calcium-channel blocking agents	DB, MC, PC, PG, RCT Patients 70 to 89 years of age with mild-to-moderate HTN (SBP 160 to 179 mm Hg and/or DBP 90 to 99 mm Hg) and MMSE scores ≥24	N=4,964 3.7 years	Primary: First major coronary event including cardiovascular death, nonfatal MI, or nonfatal stroke Secondary: cardiovascular death, nonfatal and fatal stroke and MI, cognitive function	Primary: Results showed no significant difference in the primary end point between candesartan and placebo (P=0.19). Secondary: Candesartan treatment reduced nonfatal stroke by 27.8% (P=0.04) and all stroke by 23.6% (P=0.056) compared to placebo. There were no significant differences in MI and cardiovascular mortality. Mean MMSE score fell from 28.5 to 28.0 in the candesartan group and from 28.5 to 27.9 in the control group (P=0.20). The proportion of patients who had a significant cognitive decline or developed dementia was not different in the 2 groups.
Baguet et al.[83] (2006)	DB, RCT	N=256	Primary: Change in mean	Primary: At the end of the six weeks, the mean change in DBP between the baseline and

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Candesartan 8 mg QD vs losartan 50 mg QD vs placebo	Patients with mild-to-moderate essential HTN (DBP 95 to 115 mm Hg)	6 weeks	ambulatory DBP from baseline to the 0-24 hour period after the last dose of study medication Secondary: Change in mean ambulatory SBP from baseline to the 0-24 hour period after the last dose of study medication, change in DBP and SBP during the daytime and nighttime, change in DBP and SBP between 12 and 24 hours after dosing	the 0-24 hour period after the last dose of study medication was greater in patients receiving candesartan 8 mg compared to losartan (-7.3 vs -5.1 mm Hg; P<0.05) or placebo (0.3 mm Hg; P<0.001). Secondary: The mean change in SBP between the baseline and the 0-24 hour period after the last dose of study medication was greater in patients receiving candesartan (-10.8 mm Hg) or losartan (-8.8 mm Hg) than placebo (1.2 mm Hg; P<0.001). Candesartan was associated with a greater reduction in DBP and SBP relative to placebo, when compared to losartan during both the daytime and nighttime, and between 12 and 24 hours after dosing (P<0.001). Both active treatments were well tolerated.
Ohma et al.[84] (2000) Candesartan 16 mg vs losartan 50 mg All patients received HCTZ 12.5 mg QD.	DB, MC, RCT Patients aged 20 to 80 years with mild-to-moderate uncontrolled HTN while on monotherapy (any kind of medication)	N=340 12 weeks	Primary: Change in sitting DBP Secondary: SBP, proportion of responders, safety and tolerability	Primary: Greater reductions in DBP were reported with candesartan and HCTZ vs losartan and HCTZ (-10.4 vs -7.8 mm Hg; P=0.016). Secondary: Greater decreases in SBP were reported with candesartan and HCTZ (-19.4 mm Hg) vs losartan and HCTZ (-13.7 mm Hg; P=0.004). The proportion of patients achieving a DBP ≤90 mm Hg was greater with candesartan and HCTZ (60.9 vs 49.3%; P=0.044). There were eight withdrawals due to adverse effects in the candesartan and HCTZ group and 12 in the losartan and HCTZ group. The most common adverse effects were headache, tachycardia/palpitations, dizziness, and fatigue.
Mengden et al.[85] (2011) CHILI CU Soon	MC, OL, PRO High risk patients	N=4,131 10 weeks	Primary: Change in baseline office blood	Primary: Baseline office blood pressure was 162.1±14.8/94.7±9.2 mm Hg, and after ten weeks, a reduction to 131.7±10.5/80.0±6.6 mm Hg was achieved (P<0.0001).

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Candesartan and HCTZ 32-12.5 or 32-25 mg QD (fixed-dose combination)	≥18 years of age with uncontrolled HTN, on prior antihypertensive agents, and presence of additional cardiovascular risk factors		pressure and ambulatory blood pressure, safety Secondary: Not reported	Reductions in blood pressure were comparable irrespective of prior or concurrent medications. Baseline ambulatory blood pressure was 158.2/93.7 mm Hg during the day and 141.8/85.2 mm Hg during the night. After ten weeks, ambulatory blood pressure reduced to 133.6/80.0 and 121.0/72.3 mm Hg, respectively. During the trial, 49 adverse events were reported in 1.19% of patients receiving combination therapy. Of these events, seven were regarded as serious, and most of the events were related to the nervous system or cardiac disorders. Secondary: Not reported
McInnes et al.[86] (2000) Candesartan and HCTZ 8-12.5 mg/day (fixed-dose combination product) vs lisinopril and HCTZ 10-12.5 mg/day (fixed-dose combination product)	DB, DD, MC, PG, RCT Patients 20 to 80 years of age with mild-to-moderate HTN on prior antihypertensive monotherapy	N=355 26 weeks	Primary: Mean changes in DBP Secondary: Mean changes in SBP and heart rate, proportion of responders and controlled patients, safety	Primary: Changes in mean sitting DBP did not differ significantly between the groups (mean difference, 0.5 mm Hg; P=0.20). Secondary: No significant differences between the groups were reported for mean sitting SBP, heart rate, proportion of responders and controlled patients. Both regimens were well tolerated but a greater percentage of those in the lisinopril based group (80 vs 69%) had a least one side effect (P=0.020). The proportion of patients spontaneously reporting cough (23.1 vs 4.6%) and discontinuing therapy due to adverse events (12.0 vs 5.9%) was also higher in the lisinopril based group compared to the candesartan based group.
Hosaka et al.[87] (2015) Candesartan 8 mg/ HCTZ 6.25 mg single pill combination QD	MC, OL, PRO, RCT Patients, 20 to 80 years old, with newly diagnosed, untreated hypertensive	N=206 8 weeks	Primary: Difference in home morning SBP reduction Secondary: Time-dependent	Primary: The home BP reduction at eight weeks after randomization was 11.4±1.3 mm Hg for SBP and 5.3±0.7 mm Hg for DBP in the combination group and 7.8±1.2 mm Hg for SBP and 3.6±0.6 mm Hg for DBP in the maximum dose group. Analyses using analysis of covariance adjusted by baseline home BP values as covariates showed that the combination regimen provided additional reductions of 4.0 mm Hg (95% CI, 0.8 to 7.2 mm Hg) for SBP and 1.8 mm Hg

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vs candesartan 12 mg	patients or those who were on monotherapy with any antihypertensive drug alone		changes in the antihypertensive effects and nocturnal BP reduction	(95% CI, −0.02 to 3.7 mm Hg) for DBP over the maximum dose regimen at four weeks after randomization, whereas at eight weeks after randomization, these reductions were 4.0 mm Hg (95% CI, 0.9 to 7.2 mm Hg) and 1.7 mm Hg (95% CI, −0.05 to 3.4 mm Hg), respectively. Secondary: For home nocturnal BP, the analysis included the 53 patients who measured nocturnal BP at baseline, four and eight weeks after randomization. The reduction in home nocturnal BP at eight weeks after randomization was not different between the two regimen groups. The maximal antihypertensive effect and stabilization time for home SBP were 9.4 mm Hg and 37.1 days (P<0.0001), respectively, with the combination regimen. The maximum dose regimen decreased home SBP with a very gentle slope, and estimated maximal effect and estimated stabilization time were not significant (P>0.2). The rate of achieving target BP (home morning SBP <135 mm Hg) was significantly higher with the combination regimen than with the maximum dose regimen (52.4 vs 30.1%, P=0.002).
Fogari et al.[88] (2007) CANDIA Candesartan 16 mg and HCTZ 12.5 mg QD vs amlodipine 10 mg QD	DB, MC, RCT Patients, 20 to 80 years old, with mild to moderate uncomplicated HTN not controlled on monotherapy with an antihypertensive (SBP <180 mg Hg and DBP 90 to 110 mg Hg)	N=203 8 weeks	Primary: Decrease in DBP Secondary: Sitting SBP, reduction of the orthostatic blood pressure at least two minutes after standing, change in heart rate, percentage of patients normalized (DBP <90 mm Hg and SBP <140 mm Hg), percentage of responders (reduction in DBP ≥5 mm Hg)	Primary: There was no significant difference in the mean decrease in DBP between treatment groups; the difference in final DBP was -0.02 mm Hg (95% CI, -1.48 to 1.52 mm Hg; P=0.979). Secondary: There was no significant difference between the groups at week eight for the following: sitting SBP (P=0.835), heart rate (P<0.500), orthostatic SBP (P=0.883), orthostatic DBP (P=0.264), percentage of patients normalized (P=10), percentage of responders (P=0.900). The number of patients reporting an adverse event was greater in the amlodipine group (P=0.001). The number of patients reporting an adverse drug-related event was greater in the amlodipine group (P<0.001). Changes in blood chemistry and other secondary measurements were not significantly different between the treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Gradman et al.[89] (2005) Irbesartan 150 mg QD vs aliskiren 150 to 600 mg QD vs placebo	DB, MC, PC, PG, RCT Men and women, age 18 years or older, with mild-to-moderate essential HTN (mean sitting DBP ≥95 mm Hg and <110 mm Hg)	N=652 8 weeks	Primary: Change in mean sitting DBP and SBP Secondary: Proportion of patients achieving blood pressure control (<140/90 mm Hg), safety	Primary: Decreases in mean sitting DBP at eight weeks were significantly greater with all doses of aliskiren compared to placebo (P<0.001). The least-squares mean reductions in trough DBP for aliskiren 150, 300, and 600 mg were 9.3, 11.8, and 11.5 mm Hg, respectively, vs 6.3 mm Hg for placebo. Decreases in mean sitting SBP at eight weeks were significantly greater with all doses of aliskiren compared to placebo (P<0.001). The least-squares mean reductions in trough SBP for aliskiren 150, 300, and 600 mg were 11.4, 15.8, and 15.7 mm Hg, respectively, vs 5.3 mm Hg for placebo. The antihypertensive effect of aliskiren 150 mg was comparable to irbesartan 150 mg with reductions of 8.9 and 12.5 mm Hg for mean sitting DBP and SBP, respectively. Aliskiren 300 and 600 mg produced significantly greater mean sitting DBP reductions than irbesartan 150 mg (P<0.05). While the reductions in mean sitting SBP were greater with aliskiren 300 and 600 mg than irbesartan 150 mg, these differences were not statistically significant). Secondary: The percentage of patients achieving blood pressure control was significantly greater with all doses of aliskiren (37.8%-150 mg, 50.0%-300 mg, 45.7%-600 mg) and irbesartan (33.8%) compared to placebo (20.8%; P<0.05). More patients on aliskiren 300 and 600 mg achieved blood pressure control compared to irbesartan (P<0.05). Drug-related adverse events for both aliskiren and irbesartan were comparable to placebo and the most commonly reported adverse events were headache, dizziness, and diarrhea. The number of patients discontinuing therapy was similar in all groups.
Jordan et al.[90] (2007) Irbesartan 150 to 300 mg QD, added to existing HCTZ therapy (single entity products)	DB, DD, MC, PG, RCT Obese men and women (BMI ≥30 kg/m^2) ≥18 years with essential HTN (mean sitting DBP	N=489 12 weeks	Primary: Change in mean sitting DBP with aliskiren 300 mg plus HCTZ vs HCTZ alone at 8 weeks	Primary: Aliskiren 300 mg added to HCTZ 25 mg significantly reduced mean sitting DBP compared with HCTZ alone at week eight (mean difference, -4.0; P<0.0001). Secondary: Aliskiren 300 mg added to HCTZ caused numerically larger reductions in mean sitting DBP and SBP compared with amlodipine 10 mg plus HCTZ and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs aliskiren 150 to 300 mg QD, added to existing HCTZ therapy (single entity products) vs amlodipine 5 to 10 mg QD, added to existing HCTZ therapy (single entity products) vs HCTZ 25 mg QD (existing therapy)	95 to 109 mm Hg and SBP <180 mm Hg) who had not responded to 4 weeks of treatment with HCTZ 25 mg		Secondary: Comparisons of mean sitting DBP and SBP with aliskiren plus HCTZ vs the other treatment groups, percentage of responders (mean sitting DBP <90 mm Hg or ≥10 mm Hg reduction from baseline), proportion of patients achieving blood pressure control (mean sitting blood pressure <140/90 mm Hg), plasma renin activity, safety and tolerability	irbesartan 300 mg plus HCTZ at week eight, but there were no statistically significant differences between treatment groups (P>0.05). Responder rates were significantly higher with aliskiren plus HCTZ than HCTZ alone at week eight (P=0.0193) and week 12 (P=0.004) but comparable to responder rates observed with amlodipine plus HCTZ (P>0.05) and irbesartan plus HCTZ (P>0.05). The proportion of patients achieving blood pressure control was significantly higher with aliskiren plus HCTZ than HCTZ alone at week eight (P=0.0005) and week 12 (P=0.0001) but not statistically different than amlodipine plus HCTZ (P>0.05) and irbesartan plus HCTZ (P>0.05). Plasma renin activity significantly increased (P<0.05) during four weeks of HCTZ monotherapy. Combination with aliskiren neutralized this increase and led to an overall significant reduction in plasma renin activity compared with pretreatment baseline (P<0.05) whereas amlodipine and irbesartan led to further significant increases (P<0.05). All of the study treatments were generally well tolerated. Amlodipine plus HCTZ (45.2%) was associated with a higher incidence of adverse events than the other treatment groups (36.1 to 39.3%), largely due to a higher rate of peripheral edema (11.1 vs 0.8 to 1.6%).
O'Brien et al.[91] (2007) Irbesartan 150 mg QD for 3 weeks, then aliskiren 75 mg QD added for 3 weeks, then aliskiren 150 mg QD added for 3 weeks vs	3 OL studies Men and women 18 to 80 years with ambulatory SBP ≥140 and ≤180 mm Hg without treatment	N=67 6 to 9 weeks	Primary: Change in daytime systolic ABPM with combination therapy compared with monotherapy Secondary: Change in daytime diastolic ABPM, nighttime systolic and diastolic ABPM, daytime and nighttime heart	Primary: Aliskiren coadministered with HCTZ (P=0.0007) or ramipril (P=0.03) led to significantly greater reductions in daytime systolic ABPM compared to monotherapy. There was a trend for a reduction in daytime systolic ABPM with the addition of aliskiren to irbesartan; however, this trend was not statistically significant. Secondary: Aliskiren plus HCTZ significantly lowered daytime diastolic ABPM compared to aliskiren monotherapy (P=0.0006). Changes in nighttime systolic and diastolic ABPM followed similar trends but did not achieve statistical significance (P=0.06 and P=0.09, respectively). No changes in heart rate were observed with either aliskiren regimen.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
aliskiren 150 mg QD for 3 weeks, then HCTZ 25 mg QD was added for an additional 3 weeks (if ABPM remained ≥135/85 mm Hg) vs ramipril 5 mg QD for 3 weeks, then aliskiren 75 mg QD added for 3 weeks, then aliskiren 150 mg QD added for 3 weeks			rates, plasma renin activity	Aliskiren added to irbesartan did not significantly change diastolic ABPM compared to irbesartan monotherapy; however, nighttime systolic and diastolic ABPM were significantly reduced (P<0.05 for all). No changes in heart rate were observed with either irbesartan regimen. Mean diastolic ABPM was significantly decreased with the addition of aliskiren 150 mg (P<0.05) but not aliskiren 75 mg to ramipril monotherapy. Both aliskiren doses significantly decreased nighttime systolic and diastolic ABPM (P<0.05 for all). No changes in heart rate were observed with either ramipril regimen. Aliskiren alone significantly inhibited plasma renin activity by 65% (P<0.0001), while ramipril and irbesartan monotherapy increased renin activity by 90 and 175%, respectively. When aliskiren was coadministered with HCTZ, ramipril or irbesartan, plasma renin activity remained similar to baseline levels or decreased.
Derosa et al.[92] (2005) Irbesartan 300 mg QD vs doxazosin 4 mg QD	DB, PG, RCT Patients with type 2 diabetes and mild HTN	N=96 1 year	Primary: Blood pressure, glucose metabolism and lipid parameters Secondary: Not reported	Primary: Blood pressure was significantly reduced in both treatment groups compared to baseline (P<0.01). Irbesartan was significantly better in lowering blood pressure compared to doxazosin (P<0.05). Doxazosin significantly reduced glycosylated hemoglobin, fasting plasma glucose, fasting plasma insulin, TC, LDL-C, HDL-C, and TG (P≤0.05 for all parameters). As monotherapy, neither of the drugs achieved adequate blood pressure control. Secondary: Not reported
Neutel et al.[93] (2006)	AC, DB, MC, RCT	N=737	Primary: Proportion of	Primary: Significantly more patients on combination therapy achieved seated DBP <90

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Irbesartan 150 to 300 mg QD vs irbesartan and HCTZ 150 to 300-12.5 to 25 mg QD (fixed-dose combination)	Patients ≥18 years with severe HTN who were untreated (seated DBP ≥110 mm Hg) or currently receiving antihypertensive monotherapy with DBP ≥100 mm Hg	7 weeks	patients with DBP <90 mm Hg at week 5 Secondary: Proportion of patients who achieved seated SBP/DBP <140/90 mm Hg	mm Hg at week five compared to monotherapy (47.2 vs 33.2%; P=0.0005). Secondary: Significantly more patients attained SBP/DBP <140/90 mm Hg at week five (34.6 vs 19.2%, respectively; P<0.0001), while the mean difference between combination and monotherapy in seated DBP and SBP was 4.7 and 9.7 mm Hg, respectively (P<0.0001). Greater and more rapid blood pressure reduction with irbesartan and HCTZ was achieved without additional side effects.
Neutel (abstract).[94] (2011) Irbesartan and HCTZ 150-12.5 mg QD, up titrated to 300-25 mg QD (fixed-dose combination product) vs irbesartan 150 mg QD, up titrated to 300 mg QD	Post-hoc analysis of 2 PRO, RCT Patients with uncontrolled or untreated moderate to severe HTN who are obese or who have diabetes	N=1,268 7 weeks (severe HTN) 12 weeks (moderate HTN)	Primary: Changes in baseline blood pressure, blood pressure goal rate Secondary: Safety	Primary: After seven to eight weeks of treatment, SBP/DBP decreased in patients with diabetes by 26.9/17.8 and 21.8/15.8 mm Hg with combination irbesartan and HCTZ and irbesartan treatment, respectively (P=0.09/P=0.27). In obese patients, SBP/DBP decreased by 29.4/20.2 and 20.1/15.9 mm Hg with combination irbesartan and HCTZ and irbesartan treatment, respectively (P<0.0001). More patients with type 2 diabetes achieved a blood pressure goal of <130/80 mm Hg at week seven to eight with combination irbesartan and HCTZ treatment compared to irbesartan (12 vs 5%; P=0.22). Significantly more obese patients achieved blood pressure goals with combination irbesartan and HCTZ treatment compared to irbesartan (48 vs 23%; P<0.0001). Secondary: Treatment emergent adverse event rates were similar between treatment groups regardless of the presence of diabetes or BMI status. In patients with moderate or severe HTN and with a BMI ≥30 kg/m^2, initial treatment with combination irbesartan and HCTZ was more effective compared to irbesartan.
Neutel et al.[95] (2008) Irbesartan and HCTZ 300-25 mg QD (fixed-dose combination	AC, DB, RCT Patients with moderate HTN (seated SBP 160 to 179 mm Hg when DBP <110 mm Hg;	N=538 12 weeks	Primary: Change in SBP after week 8 Secondary: Change from baseline in DBP at	Primary: At week eight, there was a reduction in SBP of 27.1 mm Hg with irbesartan and HCTZ compared to 22.1 mm Hg with irbesartan monotherapy (P=0.0016) and 15.7 mm Hg with HCTZ (P<0.0001). Secondary: At week eight, there was a reduction in DBP of 14.6 mm Hg with irbesartan

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
product) vs irbesartan 300 mg QD vs HCTZ 25 mg QD	or DBP 100 to 109 mm Hg when SBP <180 mm Hg)		weeks 8 and 12, SBP at week 12, proportion of responders (SBP <140 mm Hg and DBP <90 m Hg) at weeks 8 and 12	and HCTZ compared to 11.6 mm Hg with irbesartan monotherapy (P=0.0013) and 7.3 mm Hg with HCTZ (P<0.0001). A significantly greater percentage of patients reached a treatment goal of SBP <140 mm Hg and DBP <90 mm Hg by week eight with irbesartan and HCTZ (53.4%) compared to irbesartan (40.6%; P=0.0254) and HCTZ (20.2%; P<0.0001) alone. Treatment was well tolerated in all three treatment groups with a slight increase in adverse events in the combination therapy group.
Weir et al.[96] (2007) Irbesartan and HCTZ 300-25 mg QD (fixed-dose combination)	Pooled analysis of 2 DB, MC, RCT Patients with stage 1 or 2 HTN evaluated according to age	N=796 7 to 8 weeks	Primary: Antihypertensive efficacy, tolerability Secondary: Not reported	Primary: SBP/DBP reductions (27 to 31/16 to 22 mm Hg) were similar regardless of age, obesity and type 2 diabetes status and were greater in high- vs low-risk patients. Dizziness (2.0 to 3.7%), hypotension (0 to 0.7%), and syncope (0%) were rare and not centered in any subgroup. There was no hypotension in the elderly or in patients with type 2 diabetes. Secondary: Not reported
Bobrie et al.[97] (2005) Irbesartan and HCTZ 150-12.5 mg QD (fixed-dose combination product) vs valsartan and HCTZ 80-12.5 mg QD (fixed-dose combination product)	OL, RCT Patients whose blood pressure remained uncontrolled after 5 weeks of HCTZ 12.5 mg QD	N=464 8 weeks	Primary: Blood pressure reductions, safety Secondary: Not reported	Primary: Irbesartan and HCTZ produced greater reductions in average SBP and DBP measured by home blood pressure monitoring than valsartan and HCTZ (SBP, -13.0 vs -10.6 mm Hg; P=0.0094; DBP, -9.5 vs -7.4 mm Hg; P=0.0007). These differences were more pronounced in the morning than in the evening. Normalization rates observed with home blood pressure monitoring (SBP <135 mm Hg and DBP <85 mm Hg) were significantly greater with irbesartan and HCTZ than with valsartan and HCTZ (50.2 vs 33.2%; P=0.0003). The overall safety was similar in the two groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Stanton et al.[98] (2003) Losartan 100 mg QD vs aliskiren 37.5 to 300 mg QD	AC, DB, MC, RCT Men and women 21 to 70 years of age with mild-to-moderate HTN (SBP ≥140 mm Hg)	N=226 4 weeks	Primary: Change in daytime ambulatory SBP Secondary: Changes in clinic SBP and DBP, plasma renin activity, plasma aliskiren levels, adverse events	Primary: A dose-dependent reduction in daytime ambulatory SBP was observed with increasing aliskiren doses (with mean changes of -0.40 mm Hg with aliskiren 37.5 mg, -5.3 mm Hg with aliskiren 75 mg, -8.0 mm Hg with aliskiren 150 mg, and -11 mm Hg with aliskiren 300 mg; P=0.0002). The change in daytime SBP with losartan 100 mg (-10.9 mm Hg) was significantly different than aliskiren 37.5 mg, but not the other higher aliskiren dosages). Secondary: Clinic SBP and DBP, both in the sitting and standing positions, decreased with aliskiren in a dose-dependent manner, whereas heart rate was unaltered. The decreases in clinic blood pressures were similar for losartan 100 mg and aliskiren 150 and 300 mg. Dose-dependent reductions in plasma renin activity were also observed (median change -55, -60, -77, and -83% with 37.5, 75, 150, and 300 mg aliskiren, respectively; P=0.0008). By contrast, plasma renin activity increased by 110% with losartan 100 mg. Rate of adverse events was 22% with aliskiren 37.5 mg, 35% with aliskiren 75 mg, 25% with aliskiren 150 mg, 23% with aliskiren 300 mg, and 32% with losartan 100 mg. There was no increase in the number of adverse events when increasing the dose of aliskiren.
Ribeiro et al.[99] (2007) LAMHYST Losartan 50 to 100 mg QD vs amlodipine 5 to 10 mg QD	DB, DD, RCT Males and females, age 18 to 79 years old, with diagnosis of mild (>95 mm Hg but <115 mm Hg) to moderate essential HTN and not taking an antihypertensive medication (within last 4 weeks)	N=194 12 weeks	Primary: Difference between treatment groups in mean change in ABPM for last 9 hours of treatment and during drug holiday Secondary: Not reported	Primary: After 12 weeks, mean reductions in SBP were significantly larger in the amlodipine group than the losartan group (-18.1 vs -10.1 mm Hg; P<0.001). Mean reductions in DBP were significantly larger in the amlodipine group than the losartan group (-18.1 vs -10.1 mm Hg; P<0.05). Mean increases in SBP were similar between the groups during the two day drug holiday (P>0.05). After the two day drug holiday, SBP was lower than baseline in both groups (P<0.001), with the amlodipine group SBP remaining significantly lower (P<0.01). Mean increases in DBP were similar between the groups during the two day

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				drug holiday (P>0.05). After the two day drug holiday, DBP was lower than baseline in both groups (P=0.0001), with the amlodipine group DBP remaining significantly lower (P<0.05). Secondary: Not reported
Oparil et al.[100] (1996) Losartan 50 to 100 mg QD vs amlodipine 5 to 10 mg QD If goal DBP (≤90 mm Hg) was not attained, drug doses could be doubled and/or HCTZ mg was added.	DB, DD, MC, RCT Patients with HTN	N=900 12 weeks	Primary: Efficacy, tolerability, effects on QOL Secondary: Not reported	Primary: DBP reductions after 4, 8, and 12 weeks of therapy were clinically comparable (losartan group: 7.3, 10.4, and 11.1 mm Hg, respectively; amlodipine group: 7.9, 11.2, and 11.8 mm Hg, respectively; P value not significant). Similar reductions in SBP were seen for both treatment groups (P value not significant). The percentage of patients reaching goal DBP (≤90 mm Hg) or DBP ≥90 mm Hg with a ≥10 mm Hg decrease from baseline) was comparable for the two groups, with 68% of patients in the losartan group and 71% of patients in the amlodipine group reaching goal. Significantly more patients in the amlodipine group had drug-related adverse experiences (27 vs 13%; P=0.029). Edema was more common in patients receiving the amlodipine regimen than in those receiving the losartan regimen (11 vs 1%; P=0.004). Overall QOL was not different in the two treatment groups. Secondary: Not reported
Dahlöf et al.[101] (2002) LIFE Losartan 50 to 100 mg QD vs	DB, DD, PG, RCT Patients 55 to 80 years old with essential HTN (sitting SBP/DBP 160 to 200 to 95 to 115 mm Hg) and left ventricular	N=9,193 ≥4 years	Primary: Composite of cardiovascular death, MI and stroke Secondary: All-cause mortality, hospitalization for angina or heart	Primary: SBP fell by 30.2 and 29.1 mm Hg in the losartan and atenolol groups, respectively (treatment difference, P=0.017) and DBP fell by 16.6 and 16.8 mm Hg, respectively (treatment difference, P=0.37). MAP was 102.2 and 102.4 mm Hg, respectively (P value not significant). Heart rate decreased more in patients assigned to atenolol than losartan (-7.7 vs -1.8 beats/minute, respectively; P<0.0001). Compared to atenolol, the primary composite occurred in 13.0% fewer patients

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atenolol 50 to 100 mg QD HCTZ 12.5 to 25 mg QD was added if needed for blood pressure control.	hypertrophy		failure, revascularization procedures, resuscitated cardiac arrest, new-onset diabetes	receiving losartan (RR, 0.87; 95% CI, 0.77 to 0.98; P=0.021). While there was no difference in the incidence cardiovascular mortality (P=0.206) and MI (P=0.491), losartan treatment resulted in a 24.9% relative risk reduction in stroke compared to atenolol (P=0.001). Secondary: A 25% lower incidence of new-onset diabetes was reported with losartan compared to atenolol (P=0.001). There was no significant difference among the other secondary end points between the two treatment groups. Note: At end point or end of follow-up, 18 and 26% of patients on losartan were receiving HCTZ alone or with other drugs, respectively. In the atenolol group, 16 and 22% of patients were receiving HCTZ alone or with other drugs, respectively.
Julius et al.[102] (2004) LIFE Black Subset Losartan 50 to 100 mg QD vs atenolol 50 to 100 mg QD HCTZ 12.5 to 25 mg QD was added if needed for blood pressure control.	Post hoc analysis Patients 55 to 80 years old with essential HTN (sitting SBP/DBP 160 to 200/95 to 115 mm Hg) and left ventricular hypertrophy	N=523 ≥4 years	Primary: Composite of cardiovascular death, MI and stroke Secondary: Not reported	Primary: Compared to atenolol (11.2%), losartan in the United States African American population resulted in a greater incidence of the composite end point (17.4%; P=0.033). HRs favored atenolol across all parameters (P=0.246 for cardiovascular mortality, P=0.140 for MI, and P=0.030 for stroke). In African American patients, blood pressure reduction was similar in both groups, and regression of electrocardiographic-left ventricular hypertrophy was greater with losartan. Secondary: Not reported
Lindholm et al.[103] (2002) LIFE Diabetic Subset Losartan 50 to 100	Post hoc analysis Patients 55 to 80 years old with essential HTN (sitting SBP/DBP	N=1,195 ≥4 years	Primary: Composite of cardiovascular death, MI and stroke Secondary:	Primary: Compared to atenolol, losartan resulted in a 24% decrease in the primary composite end point (P=0.031). Losartan treatment resulted in a 37% risk reduction in cardiovascular deaths vs atenolol (P=0.028).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg QD vs atenolol 50 to 100 mg QD HCTZ 12.5 to 25 mg QD was added if needed for blood pressure control.	160 to 200/95 to 115 mm Hg) and left ventricular hypertrophy		All-cause mortality	Losartan treatment resulted in a 39% risk reduction in all-cause mortality vs atenolol (P=0.002). Mean blood pressure fell to 146/79 mm Hg in losartan patients and 148/79 mm Hg in atenolol patients. Secondary: Mortality from all causes was 63 and 104 in the losartan and atenolol groups, respectively (RR, 0.61; P=0.002).
Kjeldsen et al.[104] (2002) LIFE Isolated Systolic Hypertension Subset Losartan 50 to 100 mg QD vs atenolol 50 to 100 mg QD HCTZ 12.5 to 25 mg QD was added if needed for blood pressure control.	Post hoc analysis Patients 55 to 80 years old with isolated systolic HTN (SBP of 160 to 200 mm Hg and DBP <90 mm Hg) and left ventricular hypertrophy	N=1,326 ≥4 years	Primary: Composite of cardiovascular death, MI, or stroke Secondary: All-cause mortality	Primary: Compared to atenolol, losartan resulted in a trend towards a 25% reduction in the primary end point (P=0.06). Losartan treatment resulted in a 46% risk reduction in cardiovascular mortality (P=0.01) and 40% risk reduction in stroke compared to atenolol (P=0.02). There was no difference in the incidence of MI. Blood pressure was reduced by 28/9 and 28/9 mm Hg in the losartan and atenolol arms. Secondary: Patients receiving losartan also had reductions in all-cause mortality (28%; P<0.046).
Fossum et al.[105] (2006) ICARUS, a LIFE substudy Losartan 50 to 100 mg/day	DB, DD, PG, RCT Patients 55 to 80 years old with essential HTN (sitting SBP/DBP 160 to 200/95 to 115	N=81 3 years	Primary: Amount and density of atherosclerotic lesions in the common carotid arteries and carotid bulb	Primary: The amount of plaque decreased in the losartan group and increased in the atenolol group, though the difference between groups was not statistically significant (P=0.471). Patients in the atenolol group had a greater increase in plaque index compared to the losartan group, though the difference between groups was not

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs atenolol 50 to 100 mg/day All patients received HCTZ 12.5 to 25 mg/day if need for blood pressure control.	mm Hg) and left ventricular hypertrophy		Secondary: Not reported	statistically significant (P=0.742) Secondary: Not reported
Kizer et al.[106] (2005) LIFE substudy Losartan 50 to 100 mg/day vs atenolol 50 to 100 mg/day All patients received HCTZ 12.5 to 25 mg/day if need for blood pressure control.	DB, DD, PG, RCT Patients 55 to 80 years old with essential HTN (sitting SBP/DBP 160 to 200/95 to 115 mm Hg) and left ventricular hypertrophy	N=9,193 ≥4 years	Primary: Reduction in the risk of different stroke subtypes and neurological deficits Secondary: Not reported	Primary: The risk of fatal stroke was significantly decreased in the losartan group compared to the atenolol group (P=0.032). The risk of atherothrombotic stroke was significantly decreased in the losartan group compared to the atenolol group (P=0.001). Comparable risk reductions were observed for hemorrhagic and embolic stroke but did not reach statistical significance. The risk of recurrent stroke was significantly reduced in the losartan arm compared to the atenolol arm (P=0.017). The number of neurological deficits per stroke was similar (P=0.68), but there were fewer strokes in the losartan group for nearly every level of stroke severity. Secondary: Not reported
Wachtell et al.[107] (2005) LIFE substudy Losartan 50 to 100 mg/day	DB, DD, PG, RCT Patients 55 to 80 years old with essential HTN (sitting SBP/DBP 160 to 200/95 to 115	N=8,851 (patients in LIFE with no baseline history of atrial fibrillation	Primary: Incidence of new-onset atrial fibrillation and outcome Secondary:	Primary: Significantly fewer patients in the losartan group experienced new-onset atrial fibrillation compared to the atenolol group (P<0.001). Randomization to losartan treatment was associated with a 33% lower rate of new onset atrial fibrillation independent of other risk factors (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs atenolol 50 to 100 mg/day All patients received HCTZ 12.5 to 25 mg/day if need for blood pressure control.	mm Hg) and left ventricular hypertrophy	but at risk for atrial fibrillation) ≥4 years	Not reported	Patients in the losartan group had a 40% lower rate of composite events consisting of cardiovascular death, fatal or non-fatal stroke, and fatal or non-fatal MI (P=0.03). Significantly fewer strokes occurred in the losartan group compared to the atenolol group (P=0.01), and there was a trend toward fewer MIs in the losartan group (P=0.16). There was no significant difference in cardiovascular mortality between groups. In contrast, the atenolol group experienced significantly fewer hospitalizations for heart failure (P=0.004) and a trend toward fewer sudden cardiac deaths (P=0.07). Secondary: Not reported
Wachtell et al.[108] (2005) LIFE substudy Losartan 50 to 100 mg/day vs atenolol 50 to 100 mg/day All patients received HCTZ 12.5 to 25 mg/day if need for blood pressure control.	DB, DD, PG, RCT Patients 55 to 80 years old with essential HTN (sitting SBP/DBP 160 to 200/95 to115 mm Hg) and left ventricular hypertrophy	N=342 (LIFE patients with AF at the start of the LIFE study) ≥4 years	Primary: Cardiovascular morbidity and mortality Secondary: Not reported	Primary: Patients with a history of atrial fibrillation had significantly higher rates of cardiovascular and all-cause mortality, fatal and non-fatal stroke, heart failure, revascularization and sudden cardiac death compared to patients without atrial fibrillation (P<0.001). Patients with a history of atrial fibrillation had similar rates of MI and hospitalization for angina pectoris (P≥0.209). The primary composite endpoint of cardiovascular mortality, stroke and MI occurred in significantly fewer patients in the losartan group compared to the atenolol group (P=0.009). The difference in MI between groups was not significant. Treatment with losartan trended toward lower all-cause mortality (P=0.09) and fewer pacemaker implantations (P=0.065). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Van Bortel et al.[109] (2005) Losartan 50 mg QD vs nebivolol 5 mg QD If after 6 weeks, DBP was not normalized, then HCTZ 12.5 mg QD was added to therapy	DB, MC, PG, RCT Patients <70 years of age with DBP at randomization between 95 and 114 mm Hg	N=314 12 weeks	Primary: Effects on blood pressure, overall QOL Secondary: Comparison of different aspects of QOL	Primary: At the end of 12 weeks, both nebivolol and losartan significantly reduced SBP compared to baseline (P<0.0001 for both), but the agents were not significantly different from each other. Both agents also significantly decreased DBP compared to baseline (P<0.0001), but nebivolol significantly reduced DBP compared to losartan (P<0.02). At the end of 12 weeks, both nebivolol and losartan significantly improved QOL scores compared to baseline (P<0.007), but the agents were not significantly different from each other. Secondary: At week 12 there was not a significant difference observed in the individual questions of the QOL questionnaire between the groups. Questions inquired about headaches, lightheadedness, sleepiness, flushing, and sexual function.
Flack et al.[110] (2003) Losartan 50 mg QD vs eplerenone 50 mg QD vs placebo Doses were increased if blood pressure remained uncontrolled.	DB, MC, PG, RCT Men and women ≥18 years old, with mild to moderate HTN, with SBP <180 mm Hg and DBP 95 to 109 mm Hg (off medication) or if patients were receiving antihypertensive therapy their blood pressure was <140/90 mm Hg	N=551 16 weeks	Primary: Mean change from baseline in DBP at 16 weeks Secondary: Mean change from baseline at 16 weeks in SBP, SBP and DBP within and between racial groups, response rate (defined as the percentage of patients with DBP <90 mm Hg or DBP ≥90 mm Hg but ≥10 mm Hg below baseline), urinary albumin/creatinine ratio, effect of	Primary: At 16 weeks, patients randomized to eplerenone exhibited significantly greater mean changes in DBP from baseline compared to either losartan- or placebo-treated groups (P<0.001). Secondary: At 16 weeks, patients randomized to eplerenone exhibited significantly greater mean changes in SBP from baseline compared to either losartan- or placebo-treated groups (P<0.001). At 16 weeks, African American patients randomized to eplerenone exhibited significantly greater mean changes in SBP and DBP from baseline compared to the placebo-treated African American patients (P<0.001). At 16 weeks, African American patients randomized to eplerenone exhibited significantly greater mean changes in SBP and DBP from baseline compared to the losartan-treated African American patients (P≤0.001). At 16 weeks, white patients randomized to eplerenone exhibited significantly greater mean changes in SBP and DBP from baseline compared to the placebo-treated white patients (P=0.001). However, the difference in SBP- and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			eplerenone in patients with various baseline renin and aldosterone levels, adverse effects	DBP-lowering effects was not significant different between the eplerenone and losartan groups (P=0.126, P=0.068, respectively). Significantly greater percentage of patients randomized to eplerenone exhibited a positive response to therapy compared to either placebo (64.5 vs 41.2%; P<0.001) or losartan group (64.5 vs 48.3%; P=0.003). The eplerenone group (regardless of race) exhibited statistically significant improvement in urinary albumin/creatinine ratio from baseline compared to placebo (P=0.003). However, the difference in urinary albumin/creatinine ratio change from baseline was not significantly different between the eplerenone and losartan groups (P=0.652). Compared to losartan, eplerenone was more effective in lowering SBP and DBP in patients with low-moderate baseline renin levels (P<0.05). However, the difference was not statistically significant in patients with high baseline renin levels. Compared to losartan, eplerenone was more effective in lowering SBP in patients with low or high baseline aldosterone levels (P<0.05). However, the difference was not statistically significant in patients with moderate baseline aldosterone levels. Compared to losartan, eplerenone was more effective in lowering DBP in patients with low baseline aldosterone levels (P<0.05). However, the difference was not statistically significant in patients with moderate-high baseline aldosterone levels. There were no significant differences in the incidence of adverse events noted in eplerenone, placebo or losartan groups. The reported incidence of gynecomastia, breast pain, menstrual abnormalities, impotence, hyperkalemia and decreased libido with eplerenone was low and comparable to losartan and placebo.
Hood et al.[111] (2007) SALT	DB, RCT, XO Adult patients with seated blood	N=57 42 weeks	Primary: Change in blood pressure and plasma renin from baseline	Primary: Spironolactone 100 mg/day- and bendroflumethiazide 5 mg/day-treated patients did not exhibit a significant difference in BP reduction from baseline (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Losartan 100 mg/day vs spironolactone 50 mg/day vs spironolactone 100 mg/day vs amiloride 20 mg/day vs amiloride 40 mg/day vs bendro-flumethiazide* 2.5 mg/day vs bendro-flumethiazide* 5 mg/day vs	pressure of 140/90 to 170/110 mm Hg, plasma renin of ≤12 mU/L, plasma aldosterone-renin ratio >750, previous fall in SBP ≥20 mm Hg after 1 month of OL treatment with spironolactone 50 mg/day		between spironolactone 100 mg/day and bendro-flumethiazide 5 mg/day Secondary: Change in blood pressure and plasma renin from baseline between amiloride and other diuretics and between lower and higher doses of each diuretic	Secondary: Spironolactone 50 mg/day-treated patients exhibited a significant decrease in blood pressure from baseline compared to bendroflumethiazide 2.5 mg/day-treated patients (P<0.01). Losartan 100 mg-treated patients exhibited a significant decrease in blood pressure from baseline compared to bendroflumethiazide 2.5 mg/day-treated patients (P<0.05). High-dose bendroflumethiazide- and amiloride-treated patients exhibited significantly greater reductions in blood pressure compared to the lower doses (P<0.05). Spironolactone-treated patients exhibited a four-fold increase in baseline renin level compared to a two-fold increase observed in bendroflumethiazide-treated patients (P=0.003).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				
Maeda et al.[112] (2012) ARCH Losartan and HCTZ (fixed-dose combination product)	MC, OL, OS, PRO Patients 20 to 80 years of age with HTN uncontrolled by either ARB monotherapy or combination with and ARB and a calcium channel blocker	N=614 52 weeks	Primary: Change in blood pressure at 3 months Secondary: Not reported	Primary: Blood pressure decreased significantly to 138.0/78.2 mm Hg by month three (P<0.001), and 36.2% of patients were able to achieve target blood pressure (P<0.05). The hypotensive effect lasted for one year (P<0.001) and was found equally in patients receiving losartan-HCTZ and losartan-HCTZ plus a calcium channel blocker. Secondary: Not reported
Ueda et al.[113] (abstract) (2012) MAPPY Losartan and HCTZ 50-12.5 mg QD (fixed-dose combination product) vs losartan 100 mg QD	MC, OL, PG, PRO, RCT Patients with morning HTN	N=216 Duration not specified	Primary: Change in baseline SBP, blood pressure control rate Secondary: Safety	Primary: Morning SBP was reduced from 150.3±10.1 to 131.5±11.5 mm Hg with combination therapy (P<0.001) and from 151.0±9.3 to 142.5±13.6 mm Hg with high dose losartan therapy (P<0.001). The morning SBP reduction was significantly greater with combination therapy group compared to high dose losartan therapy (P<0.001). Combination therapy decreased evening SBP from 141.6±13.3 to 125.3±13.1 mm Hg (P<0.001), and high dose losartan therapy decreased evening SBP from 138.9±9.9 to 131.4±13.2 mm Hg (P<0.01). Although both therapies improved target blood pressure achievement rates in the morning and evening (P<0.001 for both), combination therapy significantly increased the achievement rates compared to high dose losartan therapy (P<0.001 and P<0.05, respectively). Secondary: Combination therapy decreased urine albumin excretion (P<0.05) whereas high-dose therapy reduced serum uric acid. Both therapies indicated strong adherence and few adverse effects (P<0.001).
Salerno et al.[114] (2004) Losartan and HCTZ 50-12.5 to	DB, RCT Patients with severe HTN	N=585 6 weeks	Primary: Proportion of patients achieving goal blood pressure	Primary: Almost twice as many patients achieved goal blood pressure at four weeks on losartan 50 mg and HCTZ 12.5 mg vs losartan 50 to 100 mg monotherapy (P=0.002).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
100-25 mg QD (fixed-dose combination product) vs losartan 50 to 100 mg QD Doses were titrated as needed to reach blood pressure goal (<90 mm Hg).			Secondary: Adverse events	Almost three times as many patients achieved goal blood pressure at six weeks with losartan and HCTZ vs losartan monotherapy (P<0.001). Adverse experiences on losartan and HCTZ (43%) were significantly less than with losartan monotherapy (53%).
Minami et al.[115] (2007) Losartan 50 mg/day and HCTZ 12.5 mg/day Candesartan 8 mg QD (n=10) or amlodipine 5 mg QD (n=5) administered to all patients for 2 months prior to switch to losartan plus HCTZ.	OL Japanese outpatients with essential HTN treated for ≥2 months with either candesartan or amlodipine and 24-hour ambulatory blood pressure ≥135/80 mm Hg	N=15 12 months	Primary: Changes in blood pressure Secondary: Not reported	Primary: In patients who had previously received candesartan, 24-hour blood pressure decreased significantly from 137/89 mm Hg to 126/81 mm Hg after three months (P<0.05/P<0.001) and to 123/81 mm Hg after 12 months (P<0.01/P<0.001) of treatment with losartan and HCTZ. In patients who had previously received amlodipine, 24-hour blood pressure decreased significantly from 137/81 to 125/75 mm Hg after three months (P<0.05/P<0.05) and to 124/77 mm Hg after 12 months (P<0.05/P value not significant) of treatment with losartan and HCTZ. There were significant decreases in SBP during the daytime, nighttime and early morning after 12 months in both groups. No adverse changes in the indices of glucose or lipid metabolism were observed in either group. Secondary: Not reported
Lacourcière et al.[116] (2003) PROBE	DB, MC, OL, RCT Patients ≥18 years of age with mild-to-	N=597 6 weeks	Primary: Mean changes in ambulatory DBP	Primary: During the last six hours of the dosing interval, telmisartan 40 mg and HCTZ 12.5 mg and telmisartan 80 mg and HCTZ 12.5 mg reduced mean DBP to a greater extent vs losartan 50 mg and HCTZ 12.5 mg. Treatment differences

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Losartan and HCTZ 50-12.5 mg QD (fixed-dose combination product) vs telmisartan and HCTZ 40-12.5 mg QD (fixed-dose combination product) vs telmisartan and HCTZ 80-12.5 mg QD (fixed-dose combination product)	moderate essential HTN		Secondary: Mean changes in ambulatory SBP, 24-hour DBP, safety	between the groups were 1.8 mm Hg (P<0.05) and 2.5 mm Hg (P<0.001) lower, respectively, with the telmisartan and HCTZ arms. Secondary: Telmisartan 40 mg and HCTZ 12.5 mg and telmisartan 80 mg and HCTZ 12.5 mg produced greater reductions in ambulatory SBP vs losartan 50 mg and HCTZ 12.5 mg of 2.5 and 3.4 mm Hg, respectively, during the last six hours of the dosing interval (P<0.05), and of 2.1 and 3.4 mm Hg, respectively, over the entire 24-hour dosing interval (P<0.05). Telmisartan 80 mg and HCTZ 12.5 mg also lowered mean 24-hour DBP by 2.3 mm Hg more than losartan 50 mg and HCTZ 12.5 mg (P<0.001). All treatments were well tolerated.
Brunner et al.[117] (2006) Olmesartan 20 mg QD vs candesartan 8 mg QD	DB, RCT Patients with mainly mild-to-moderate HTN	N=635 8 weeks	Primary: 24-hour antihypertensive efficacy (with particular emphasis on blood pressure control during the early morning period), proportion of patients who achieved various ABPM goals (SBP/DBP <125/80 mm Hg) Secondary:	Primary: After eight weeks, significantly greater proportions of patients treated with olmesartan achieved 24-hour and daytime ABPM goals 25.6 and 18.3%, respectively) compared to candesartan (14.9%; P<0.001 and 9.6%; P=0.002, respectively). During the last four hours of 24-hour ABPM, the proportion of patients who achieved goals was significantly greater with olmesartan (33.3%) than candesartan (22.9%; P<0.001). Similarly, during the last two hours of 24-hour ABPM, the proportion of patients who achieved these blood pressure goals was higher with olmesartan (26.9 and 19.9%) compared to candesartan (19.6%; P=0.028 and 14.3%; P=0.061). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Not reported	Not reported
Punzi et al.[118] (2012) Olmesartan 20 mg QD, up titrated to 40 mg QD vs losartan 50 mg QD, up titrated to 100 mg QD	DB, PRO, RCT Patients with HTN no previously treated or previously treated with antihypertensive medications	N=941 8 weeks	Primary: Change in baseline seated cuff DBP at week 8 Secondary: Mean change in seated cuff SBP at weeks 4 and 8 and seated cuff DBP at week 4, blood pressure target rates, safety	Primary: Olmesartan produced significantly greater LSM reductions in seated cuff DBP compared to losartan in treatment-naïve (-9.7±1.0 vs -6.6±1.0 mm Hg; P=0.0232) and treatment-experienced patients (-9.6±0.5 vs -7.3±0.5 mm Hg; P=0.0013). Secondary: Both treatment-naïve (-12.1±1.2 vs -8.5±1.3 mm Hg; P=0.0379) and treatment-experienced patients (-12.0±0.7 vs -8.5±0.7 mm Hg; P=0.0006) receiving olmesartan had significantly greater reductions in baseline cuff seated SBP compared to losartan at week 4. Similar results were observed at week eight (P=0.0178 and P=0.0016). A similar trend in significantly greater baseline reductions with olmesartan compared to losartan was observed at week four for seated cuff DBP in treatment-naïve (LSM difference, -2.3±1.10; P=0.0337) and treatment-experienced patients (LSM difference, -2.7±0.67; P<0.0001). A significantly greater proportion of treatment-naïve patients receiving olmesartan achieved a seated cuff blood pressure goal of <140/90 mm Hg with olmesartan compared to losartan (34.1 vs 19.0%; P=0.0109). Similar results were observed in treatment-experienced patients (31.0 vs 19.6%; P=0.0008). Treatment-emergent adverse events were reported in 30.5 and 31.4% of treatment-naïve and treatment-experienced patients receiving olmesartan. Corresponding proportions for losartan were 33.0 and 31.2%. Most events were mild to moderate in severity.
Oparil et al.[119] (2001) Olmesartan 20 mg QD vs irbesartan 150 mg	DB, MC, PG, RCT Patients ≥18 years old (mean age 52 years) with essential HTN (cuff DBP ≥100 mm Hg and ≤115 mm Hg and mean daytime DBP	N=588 8 weeks	Primary: Change in seated cuff DBP at week 8 Secondary: Change in seated cuff SBP at week 8, 24-hour DBP and SBP, adverse events	Primary: The mean reductions in seated cuff DBP at week eight were significantly greater with olmesartan (11.5 mm Hg) than with irbesartan (9.9 mm Hg; P=0.0412), losartan (8.2 mm Hg; P=0.0002) and valsartan (7.9 mm Hg; P<0.0001). The clinical significance of a few mm Hg DBP difference between the groups is unknown.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD, losartan 50 mg QD, or valsartan 80 mg QD	≥90 mm Hg and <120 mm Hg)			Secondary: Reductions of cuff SBP were not significantly different among the four ARBs and ranged from 8.4 to 11.3 mm Hg. The reduction in mean 24-hour DBP with olmesartan (8.5 mm Hg) was significantly greater than reductions with losartan and valsartan (6.2 and 5.6 mm Hg, respectively) and showed a trend toward significance when compared to irbesartan (7.4 mm Hg; P=0.087). The reduction in mean 24-hour SBP with olmesartan (12.5 mm Hg) was significantly greater than the reductions with losartan and valsartan (9.0 and 8.1 mm Hg, respectively) and equivalent to the reduction with irbesartan (11.3 mm Hg). All drugs were well tolerated with the incidence of adverse events reported in 30.6% of patients in the olmesartan group, 35.6% for irbesartan, 32.0% for losartan, and 44.8% for valsartan.
Chrysant et al.[120] (2004) Olmesartan 10 to 40 mg QD and HCTZ 12.5 to 25 mg QD vs olmesartan 10 to 40 mg QD vs HCTZ 12.5 to 25 mg QD vs	DB, RCT, factorial design Patients with a baseline mean seated DBP of 110 to 115 mm Hg	N=502 8 weeks	Primary: Change in DBP at week 8 Secondary: Change in SBP at week 8	Primary: Olmesartan and HCTZ produced greater reductions in seated DBP at week eight than did monotherapy with either component. All olmesartan and HCTZ combinations significantly reduced DBP compared to placebo in a dose-dependent manner. Reductions in mean trough DBP were 8.2, 16.4, and 21.9 mm Hg with placebo, olmesartan 20 mg plus HCTZ 12.5 mg, and olmesartan 40 mg plus HCTZ 25 mg, respectively. Secondary: Olmesartan and HCTZ produced greater reductions in seated SBP at week eight than did monotherapy with either component. All olmesartan and HCTZ combinations significantly reduced DBP compared to placebo in a dose-dependent manner. Reductions in mean trough SBP were 3.3, 20.1, and 26.8 mm Hg with placebo, olmesartan 20 mg plus HCTZ 12.5 mg, and olmesartan 40 mg plus HCTZ 25 mg, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				All treatments were well tolerated.
Kereiakes et al.[121] (2007) Benazepril 10 mg/day for 2 weeks, then 20 mg/day for 2 weeks, then benazepril 20 mg/day plus amlodipine 5 mg/day for 4 weeks, then benazepril 20 mg/day plus amlodipine 10 mg/day for 4 weeks vs olmesartan 20 mg/day for 2 weeks, then 40 mg/day for 2 weeks then olmesartan and HCTZ 40-12.5 mg/day for 4 weeks increased to 40-25 mg for 4 weeks	DB, DD, MC, PG, RCT Patients with stage 2 HTN	N=190 12 weeks	Primary: Change in mean seated SBP at the end of week 12 Secondary: DBP at the end of week 12, percent of patients attaining blood pressure goals of <140/90, <130/85, and <130/80 mm Hg	Primary: Patients treated with olmesartan and HCTZ experienced significantly greater reductions in mean seated SBP at week 12 than patients treated with benazepril plus amlodipine (least square mean change, -32.5 vs -26.5 mm Hg; P=0.024; least square mean treatment difference, -6.0 mm Hg; 95% CI, -11.1 to -0.8). Secondary: The least square mean change for reduction in DBP approached statistical significance with olmesartan and HCTZ compared to benazepril plus amlodipine at week 12 (P=0.056). The percentage of patients achieving goal rates at the end of the study for olmesartan and HCTZ and benazepril plus amlodipine were 66.3 and 44.7% (P=0.006) for <140/90 mm Hg, 44.9 vs 21.2% (P=0.001) for <130/85 mm Hg, and 32.6 and 14.1% (P=0.006) for <130/80 mm Hg. Both treatments were well tolerated.
Chrysant et al.[122] (2008) COACH	DB, MC, PC, RCT Patients, age 18 years and older,	N=1,940 8 weeks	Primary: Change from baseline in seated DBP at week 8	Primary: All active treatments and placebo resulted in significant decreases in seated DBP at week eight (P<0.001). Reductions in seated DBP with monotherapy treatment ranged from -8.3 to -12.7 mm Hg; reductions with combination

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Olmesartan 10 to 40 mg QD vs amlodipine 5 to 10 mg QD vs olmesartan 10 to 40 mg and amlodipine 5 to 10 mg QD vs placebo	with seated DBP of 95 to 120 mm Hg		Secondary: Change from baseline in seated SBP at week 8, mean change from baseline in seated DBP and SBP at weeks 2, 4, 6 and 8 without last observation carried forward, proportion of patients achieving BP goal (<140/90 mm Hg or <130/80 mm Hg), safety	therapy ranged from -13.8 to -19.0 mm Hg. All combinations reduced seated DBP significantly greater than either component as monotherapy at the same dosage (P<0.001). Secondary: All active treatments and placebo resulted in significant decreases in seated SBP at week eight (P<0.001 for treatment, P=0.024 for placebo). All combinations reduced seated SBP significantly greater either component as monotherapy at the same dosage (P<0.001). The proportion of patients achieving goal blood pressures were: 20.0 to 36.3% of patients receiving olmesartan monotherapy, 21.1 to 32.5% of patients receiving amlodipine monotherapy, 35.0 to 53.2% of patients receiving combination therapy, and 8.8% of patients receiving placebo. Combination therapy resulted in significantly greater achievement of goal blood pressure than monotherapy (P<0.005). No difference in overall rates of adverse events across the different treatment groups was seen. Nearly 27% of patients experienced a drug-related adverse event. Changes in laboratory values were not considered clinically significant nor followed a consistent pattern with treatment: none of the changes were considered clinically significant. Platelet counts increased significantly from baseline (statistically) for patients receiving amlodipine, however the increase was <10% and not deemed clinically relevant.
Chrysant et al.[123] (2009) COACH Olmesartan 10 to 40 mg QD and amlodipine 5 to 10 mg QD HCTZ 12.5 to 25	OL, ES Patients ≥ 18 years of age with essential HTN (seated DBP ≥95and <120 mm Hg)	N=1,684 44 weeks OL therapy (52 weeks total study duration including 8 week DB phase)	Primary: Reduction in mean sitting SBP DBP, change in mean sitting SBP and DBP, percentage of patients achieving blood pressure goal (<140/90 mm Hg or	Primary: Mean sitting DBP decreased from 101.5 mm Hg at baseline to 81.9 mm Hg and mean sitting SBP decreased from 163.6 mm Hg at baseline to 131.2 mm Hg at week 52. Approximately 31% of patients remained on amlodipine 5 mg and olmesartan 40 mg. Increasing the dose of amlodipine to 10 mg in combination with olmesartan 40 mg produced further decreases in mean sitting DBP of 4.8 mm Hg and mean sitting SBP of 7.3 mm Hg. Addition of HCTZ 12.5 mg to amlodipine 10 mg and olmesartan 40 mg decreased mean sitting DBP by 4.5

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg could be added if blood pressure was not controlled (<140/90 mm Hg or <130/80 mm Hg in patients with diabetes).			<130/80 mm Hg for patients with diabetes)	mm Hg and mean sitting SBP by 7.7 mm Hg. Doubling the HCTZ dose from 12.5 to 25 mg decreased mean sitting DBP and mean sitting SBP by an additional 6.0 mm Hg and 9.9 mm Hg, respectively. Patients who received the triple therapy had the greatest mean sitting SBP reduction (36.1 mm Hg). Approximately 67% of patients achieved blood pressure goal by week 52. The blood pressure goal achievement was 80% for amlodipine and olmesartan 5/40 mg, 70.6% for amlodipine and olmesartan 10/40 mg, 66.6% for amlodipine and olmesartan and HCTZ 10/40/12.5 mg, and 46.3% for amlodipine and olmesartan and HCTZ 10/ 40/25 mg. The addition of HCTZ 25 mg enabled more patients to achieve blood pressure targets of <140⁄90 mm Hg (77.7%), <130⁄85 mm Hg (47.5%), and <130⁄80 mm Hg (36.4%) compared to the other treatment regimens. No major safety issues emerged with long-term therapy. The frequency of edema ranged from 8.9% in patients treated with amlodipine 5 mg and olmesartan 40 mg to 14.5% in patients treated with amlodipine 10 mg and olmesartan 40 mg plus HCTZ 25 mg. Other treatment-emergent adverse events experienced by ≥3% of patients included upper respiratory tract infection (6.5%), nasopharyngitis (5.2%), extremity pain (4.1%), sinusitis (3.6%), arthralgia (3.3%), and back pain (3.1%). headache (2.0%), hypotension (1.8%), and fatigue (1.6%). The incidence of cough was 0.4%.
Oparil et al.[124] (2009) COACH Amlodipine 5 to 10 mg QD and olmesartan 10 to 40 mg vs amlodipine 5 to 10 mg QD	DB, factorial, MC, PC, RCT Patients ≥18 years of age with seated DBP 95 to 120 mm Hg, with a subgroup analysis based on HTN (stage 1: SBP 140 to 159 mm Hg or DBP 90 to 99 mm Hg; stage 2: SBP ≥160 mm Hg or DBP ≥100 mm Hg)	N=1,940 8 weeks	Primary: Mean change in DBP and SBP at week 8 for each subgroup Secondary: Proportion of patients achieving blood pressure goal (<140/90 mm Hg or <130/80 mm Hg)	Primary: Reductions in mean DBP as a result of combination treatment were similar between subgroups. Patients with stage 1 HTN achieved reductions of 14.8 to 15.8 mm Hg and patients with stage 2 HTN achieved reductions of 13.6 to 19.8 mm Hg. Reductions in mean SBP as a result of combination treatment resulted in greater reductions in patients with stage 2 HTN (25.1 to 32.7 mm Hg) compared to stage 1 HTN (17.7 to 23.7 mm Hg) (P value not reported). Reductions in mean DBP and SBP were similar between those with no prior antihypertensive treatment and those with prior hypertensive treatment. Secondary: The proportion of patients with stage 1 HTN who received combination treatment and achieved blood pressure goal was 65.6 to 80.0%, compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs olmesartan 10 to 40 mg QD vs placebo	and no prior antihypertensive medication			40.5 to 66.7% of those who received monotherapy (P<0.0001 across treatments). The proportion of patients with stage 2 HTN who received combination treatment and achieved BP goal was 40.5 to 49.2%, compared to 13.1 to 29.2% of those who received monotherapy (P<0.0001). Results of patients with baseline SBP ≥180 mm Hg were similar to other subgroups.
Braun et al.[125] (abstract) (2009) Amlodipine 10 mg plus olmesartan 20 mg QD If patients were uncontrolled after 4 weeks, they were changed to amlodipine and valsartan 10-160 mg QD.	OL, PRO Patients with DBP 100 to 109 mm Hg	N=257 8 weeks	Primary: Reduction in SBP and DBP Secondary: Adverse events	Primary: Following treatment with amlodipine and olmesartan, SBP/DBP decreased by 19.2±12.4/14.4±7.4 mm Hg. The number of patients who progressed to treatment with amlodipine and valsartan was 175. Additional reductions in SBP of 7.9 mm Hg and DBP of 3.9 mm Hg were seen (P<0.0001 for both). Secondary: Both treatments were well tolerated and reported adverse events were consistent with drug profiles.
Chrysant et al.[126] (2012) TRINITY Olmesartan and amlodipine and HCTZ 40-10-25 mg/day (fixed-dose combination product) vs	DB, MC, PG, RCT Patients ≥18 years of age with mean sitting blood pressure ≥140/100 mm Hg or ≥160/90 mm Hg (off antihypertensive medication)	N=2,492 12 weeks	Primary: Change in baseline mean sitting DBP Secondary: Change in baseline mean sitting SBP, blood pressure goal rate, safety	Primary: In both Black and non-Black patients, triple combination treatment resulted in significantly greater reductions in mean sitting DBP compared to combination therapies (P≤0.0001). Overall, triple combination treatment reduced LSM mean sitting blood pressure by -37.1/20.8 and -38.9/21.8 mm Hg in Black and non-Black patients at week 12 (P<0.0001 vs combination therapies). Secondary: In both Black and non-Black patients, triple combination treatment resulted in significantly greater reductions in mean sitting SBP compared to combination therapies (P<0.0001). A significantly greater proportion of patients receiving triple combination

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
component dual-combination treatments				treatment achieved blood pressure goal compared to combination therapies, regardless of race. No new safety concerns were identified with any treatment. The majority of treatment emergent adverse events were mild to moderate in severity. Treatment emergent adverse events occurred in 366 (52.0%) and 921 (57.6%) Black and non-Black patients.
Chrysant et al.[127] (abstract) (2012) TRINITY Olmesartan and amlodipine and HCTZ 40-10-25 mg/day (fixed-dose combination product) vs component dual-combination treatments	Subgroup analysis Patients ≥18 years of age with HTN and diabetes	N=not reported 12 weeks	Primary: Change in baseline blood pressure, blood pressure control rate Secondary: Safety	Primary: The prespecified changes in blood pressure from baseline for the diabetes subgroup receiving triple combination treatment were significantly greater compared to the dual-combination treatments (P≤0.0013). Significantly more patients with diabetes receiving triple combination treatment achieved goal blood pressure (<130/80 mm Hg) compared to patients receiving dual combination treatments (P≤0.0092). Secondary: Most treatment-emergent adverse events were mild to moderate in severity.
Kereiakes et al.[128] (2011) TRINITY Olmesartan and amlodipine and HCTZ 40-10-25 mg/day (fixed-dose combination product) vs	ES, OL Patients ≥18 years of age with mean sitting blood pressure ≥140/100 mm Hg or ≥160/90 mm Hg (off antihypertensive medication)	N=2,112 40 weeks	Primary: Efficacy, safety Secondary: Not reported	Primary: Mean changes in blood pressure from baseline to week 52 were comparable for all treatments. The proportion of patients receiving triple combination treatment who achieved blood pressure goals at week 52 ranged between 44.5 to 79.8% depending on the dose; lower doses were associated with a smaller proportion of patients achieving blood pressure goals. No new safety concerns were identified. Most adverse events and drug-related adverse events were considered to be of mild to moderate severity. One hundred and six patients reported a serious adverse event and five drug-related adverse events. Serious drug-related adverse events included acute renal insufficiency, presyncope, and hypotension in three patients; acute renal insufficiency with hyperkalemia in one patients; and syncope in one patient.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
component dual-combination treatments				Secondary: Not reported
Punzi, HA[129] (2014) Once daily olmesartan medoxomil (OM)/ amlodipine besylate (AM)/ HCTZ 40/10/25 mg	OL, PRO, blinded-endpoint Adults on 1, 2, or 3 antihypertensive medications and not at goal BP, defined as less than 140/90 mmHg or less than 130/80 mmHg if they had diabetes or renal disease	N=40 2 to 9 day screening period, followed by 4 to 6 weeks of open-label treatment	Primary: Mean change from baseline in 24 hour SBP ABPM at day 1 Secondary: Mean change from baseline in 24 hour DBP ABPM at day 1, the change from baseline in mean trough seated BP at weeks 1, 2, 3, and 4	Primary: At day 1, treatment with OM/AM/HCTZ resulted in a significant mean reduction from baseline in ambulatory SBP reduction of 5.55 ± 1.3 mmHg (P<0.0001). Secondary: Significant proportion of patients (90%) receiving OM/AM/HCTZ achieved the seated BP goal of < 140/90 mmHg at week 4, with 97% achieving <140 mmHg. The proportion of patients achieving the 24 hour ambulatory BP target of <130/80 mmHg was 84% at week 4. At day 1, for the secondary endpoints, treatment with OM/AM/HCTZ resulted in a significant mean reduction from baseline in ambulatory DBP of 2.55 ± 1.0 (P<0.0052), seated cuff SBP reduction of 9.78 ± 1.5 (P<0.0001), and seated cuff DBP reduction of 4.13 ± 1.4 (P<0.0052).
Sharma et al.[130] (2012) Telmisartan vs placebo All patients are receiving amlodipine	DB, PG, RCT Patients with type 2 diabetes and stage 1 or 2 HTN	N=981 8 weeks	Primary: Change in mean seated trough cuff SBP at weeks 8 Secondary: Blood pressure goal rates; change in mean seated trough cuff SBP at weeks 1, 2, and 4; safety	Primary: After eight weeks, significantly greater reductions in mean seated trough cuff SBP was achieved with telmisartan compared to placebo (-29.0 vs -22.9 mm Hg; P<0.0001). Secondary: After eight weeks, 71.4 and 53.8% of patients achieved blood pressure goal (<140/90 mm Hg) with telmisartan compared to placebo. A blood pressure goal of <130/80 mm Hg was achieved by 36.4 and 17.9% of patients receiving telmisartan and placebo. Significant reductions in mean seated trough cuff SBP with telmisartan were evidence from week one (P<0.0001) and continued throughout the trial. The most common adverse events were peripheral edema, headache, and dizziness.
Williams et al.[131] (2009)	Pooled analysis: blinded endpoint,	N=1,613	Primary: Change from	Primary: A significantly greater reduction in mean ambulatory blood pressure during

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PRISMA I and PRISMA II Ramipril 2.5 mg QD for 2 weeks then force titration to 5 mg QD for 6 weeks then 10 mg QD for 6 weeks vs telmisartan 40 mg QD for 2 weeks then force titration to 80 mg QD for 12 weeks	OL, PRO, RCT Patients ≥18 years of age with mild- to moderate HTN	14 weeks	baseline in mean ambulatory BP during the final 6 hours of the 24-hour dosing interval Secondary: Change from baseline in mean ambulatory blood pressure during the 24-hour dosing interval, morning, daytime and nighttime ambulatory blood pressure, 24-hour blood pressure load, treatment response, blood pressure control	the last six hours of the 24-hour dosing interval was observed with telmisartan 80 mg group compared to ramipril 5 and 10 mg (P<0.0001). Secondary: Significantly greater reductions in mean 24-hour, morning, daytime, nighttime and 24-hour blood pressure load were observed with telmisartan 80 mg compared to ramipril 5 and 10 mg (P<0.0001). Significantly greater reductions in treatment response and blood pressure control rates were observed with telmisartan 80 mg compared to ramipril 5 and 10 mg (P<0.0001).
Karlberg et al.[132] (1999) TEES Enalapril 5 to 20 mg QD vs telmisartan 20 to 80 mg QD HCTZ 12.5 or 25 mg QD could be added to either group as needed to	DB, DD, MC, PG, RCT Patients ≥65 years of age with mild- to moderate HTN	N=278 26 weeks	Primary: Change from baseline in supine SBP and DBP Secondary: Proportion of responders, safety	Primary: Both treatments had similar rates of HCTZ use. Both treatments showed comparable decreases in blood pressure. Mean changes in DBP were -12.8 mm Hg for telmisartan and -11.4 mm Hg for enalapril (P=0.074). Mean changes in SBP were -22.1 mm Hg for telmisartan and -20.1 mm Hg for enalapril (P=0.350). Secondary: Overall, 63 and 62% of patients responded to telmisartan and enalapril, respectively, with a DBP of <90 mm Hg. Both regimens provided effective blood pressure lowering over the 24-hour dosing interval, as determined by ambulatory blood pressure monitoring. Both regimens were well tolerated; however, the enalapril group had a higher incidence of cough than the telmisartan group (15.8 vs 6.5%; P value

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
reach DBP goal (≤90 mm Hg)				reported).
Xi et al.[133] (2008) Telmisartan vs losartan	MA Patients with HTN	N=1,832 (11 trials) Variable duration	Primary: Reduction in DBP and SBP Secondary: Therapeutic response of DBP and SBP, tolerability	Primary: Use of telmisartan resulted in a significant reduction in clinic DBP (WMD, 1.52; 95% CI, 0.85 to 2.19) and SBP (WMD, 2.77; 95% CI, 1.90 to 3.63) when compared to losartan. Secondary: There was also a significant reduction in 24-hour mean ambulatory DBP (WMD, 2.49; 95% CI, 0.56 to 4.42) and SBP (WMD, 2.47; 95% CI, 0.40 to 4.55) with telmisartan as compared to losartan. There was a significant increase in therapeutic response of DBP (RR, 1.14; 95% CI, 14 to 1.23) and SBP response (RR, 1.10; 95% CI, 11 to 1.20) with telmisartan as compared to losartan. Both telmisartan and losartan were well tolerated.
Sharma et al.[134] (2007) Telmisartan and amlodipine 40-5 mg QD (fixed-dose combination) vs amlodipine 5 mg QD	DB, MC, RCT Patients 18 to 65 years of age with established stage II uncomplicated essential HTN	N=210 12 weeks	Primary: SBP/DBP reductions and responder rates (SBP/DBP <130/<80 mm Hg) Secondary: Not reported	Primary: There was a significant reduction from baseline in mean SBP in both groups (telmisartan and amlodipine, from 176.3 to 128.0 mm Hg; amlodipine, from 171.8 to 143.4 mm Hg; both, P<0.05 vs baseline). There was a significant reduction in SBP from baseline in the telmisartan and amlodipine and amlodipine groups (-27.4% and -16.6%, respectively; P<0.05 within group and between groups). There was a significant reduction from baseline in mean DBP in both treatment groups (telmisartan and amlodipine, from 100.9 to 93.8 mm Hg; amlodipine, from 99.7 to 94.3 mm Hg; both, P<0.05). There was a 20.2% reduction in mean DBP in the telmisartan and amlodipine group, which was significantly greater compared to the reduction of 12.7% observed in the amlodipine group (P<0.05 between groups and within both groups). A total of 87.3% of patients receiving telmisartan and amlodipine reached the target SBP/DBP goal, compared to 69.3% of patients receiving amlodipine (P<0.05). A total of 16.0% of patients in the telmisartan and amlodipine group

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				experienced adverse events compared to 15.4% of patients in the amlodipine group (P value not significant). The most common adverse events in the telmisartan and amlodipine group were peripheral edema (8.5%), headache (5.7%), dizziness and cough (3.8%), and diarrhea (1.9%). Secondary: Not reported
Littlejohn et al.[135] (2009) Telmisartan 20 to 80 mg and amlodipine 2.5 to 10 mg QD vs telmisartan 20 to 80 mg QD vs amlodipine 2.5 to 10 mg QD vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with Stage 1 or 2 HTN (DBP ≥95 and ≤119 mm Hg)	N=2,607 8 weeks	Primary: Change in the in-clinic seated diastolic BP Secondary: Change in the in-clinic seated SBP, DBP and SBP response (DBP <90 mm Hg, decrease in DBP ≥10 mm Hg, SBP <140 mm Hg, decrease in SBP ≥15 mm Hg), and BP control (DBP <90 mm Hg and SBP <140 mm Hg)	Primary: Both telmisartan (irrespective of amlodipine dosage; P<0.0001) and amlodipine (irrespective of telmisartan dosage; P<0.0001) significantly lowered the in-clinic DBP. The greatest reduction in blood pressure was with telmisartan 80 mg plus amlodipine 10 mg (SBP/DBP -26.4/-20.1 mm Hg; P<0.05 vs both monotherapies). DBP and SBP response was achieved by 91.2 and 90.4% of patients in the telmisartan 80 mg plus amlodipine 10 mg group, respectively. More than 50% of patients treated with combination therapy achieved blood pressure control, with the highest percentages (76.5% [overall control] and 85.3% [DBP control]) being achieved by patients treated with telmisartan 80 mg plus amlodipine 10 mg. A total of 37.3% of patients reported at least one adverse event. The most commonly reported adverse events were headache (5.4%) and peripheral edema (4.4%). Headache was more frequent in the placebo group (10.9%) compared to the telmisartan monotherapy (5.9%), amlodipine monotherapy (6.0%), and combination therapy (4.7%). The incidence of peripheral edema was highest in the amlodipine 10-mg group (17.8%); however, this rate was lower when amlodipine was used in combination with telmisartan: 11.4% (telmisartan 20 mg and amlodipine 10 mg), 6.2% (telmisartan 40 mg and amlodipine 10 mg), and 11.3% (telmisartan 80 mg and amlodipine 10 mg).
Littlejohn et al.[136] (2009) Telmisartan and	DB, DD, MC, PC, PG, RCT Patients ≥18 years	N=1,078 8 weeks	Primary: Change in DBP from baseline to study end point	Primary: Significant reductions in DBP were seen from baseline to study end for both dual therapy and monotherapy (P values not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
amlodipine 40-5 mg QD (fixed-dose combination product) vs telmisartan and amlodipine 40-10 mg QD (fixed-dose combination product) vs telmisartan and amlodipine 80-5 mg QD (fixed-dose combination product) vs telmisartan and amlodipine 80-10 mg QD (fixed-dose combination product) vs respective monotherapies, dosing frequency not specified	of age with stage 1 or 2 HTN (DBP ≥95 and ≤119 mm Hg), with a subgroup analysis including patients with DBP ≥100 mm Hg at baseline		Secondary: Change from baseline to study end in SBP; percent of patients achieving a DBP response (DBP <90 mm Hg) and SBP response (SBP <140 mm Hg or reduction from baseline ≥15 mm Hg); percent of patients achieving BP control (SBP/DBP <140/<90 mm Hg) and DBP control (<90 mm Hg) and safety	Amlodipine 5 and 10 mg with telmisartan 40 and 80 mg significantly reduced DBP compared to respective monotherapies (P values not reported). Secondary: Amlodipine 5 and 10 mg with telmisartan 40 and 80 mg significantly reduced SBP compared to respective monotherapies (P values not reported). Combination therapy resulted in a greater DBP and SBP response than monotherapy (P values not reported). The highest rate of BP control was achieved with amlodipine 10 mg with telmisartan 80 mg. Rates of adverse events were similar between dual therapy and monotherapy. Incidences of adverse events were 4.40% with telmisartan monotherapy, 11.00% with amlodipine monotherapy and 11.75% with combination therapy. The most commonly reported events were headache and peripheral edema. Patients receiving amlodipine 10 mg had the highest incidence of peripheral edema; however rates were lower when amlodipine was used in combination with telmisartan.
Neutel et al.[137]	DB, MC, PG, RCT	N=858	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2012) TEAMSTA Telmisartan and amlodipine 80-10 mg QD (fixed-dose combination product) vs telmisartan 80 mg QD vs amlodipine 10 mg QD	Patients ≥18 years of age with severe HTN	8 weeks	Change in baseline blood pressure, blood pressure goal and response rates Secondary: Safety	Reductions in seated trough cuff blood pressure (-47.5/-18.7 mm Hg) were significantly greater with combination therapy compared to telmisartan (P<0.001) or amlodipine (P=0.002). Significant reductions with combination therapy were observed at one, two, four, and six weeks. Blood pressure goal and response rates were consistently higher with combination therapy (50.4 and 91.4 to 99.7%) compared to monotherapy with either agent (24.1 and 69.3 to 91.5% and 35.6 and 83.9 to 98.5%). Secondary: Combination therapy was well tolerated and fewer adverse events were reported with combination therapy compared to amlodipine (12.6 vs 16.4%). Peripheral edema was reported more frequently with amlodipine compared to combination therapy (13.2 vs 9.3%).
Oparil et al.[138] (2007) Aliskiren 150 to 300 mg QD vs valsartan 160 to 320 mg QD vs aliskiren 150 to 300 mg and valsartan 160 to 320 mg QD vs	DB, MC, PC, RCT Men and women aged 18 years or over with stage 1-2 essential HTN (mean sitting DBP 95 to 109 mm Hg and 8-hr ambulatory DBP ≥90 mm Hg)	N=1,797 8 weeks	Primary: Change in mean sitting DBP Secondary: Change in mean sitting SBP, proportion of patients achieving a successful response to treatment (mean sitting DBP <90 mm Hg and/or ≥10 mm Hg reduction from baseline) or achieving blood pressure control (mean sitting SBP/DBP <140/90	Primary: The combination of aliskiren 300 mg and valsartan 320 mg lowered mean sitting DBP from baseline by 12.2 mm Hg, significantly more than either monotherapy with aliskiren 300 mg (-9.0 mm Hg; P<0.0001), valsartan 320 mg (-9.7 mm Hg; P<0.0001) or with placebo (-4.1 mm Hg; P<0.0001). Monotherapy with aliskiren or valsartan provided significantly greater reductions in mean sitting DBP than did placebo at week 8 (P<0.0001 for all). Secondary: The combination of aliskiren 300 mg and valsartan 320 mg lowered mean sitting SBP from baseline by 17.2 mm Hg, significantly more than either monotherapy with aliskiren 300 mg (-13.0 mm Hg; P<0.0001), valsartan 320 mg (-12.8 mm Hg; P<0.0001), or with placebo (-4.6 mm Hg; P<0.0001). Monotherapy with aliskiren or valsartan provided significantly greater reductions in mean sitting SBP than did placebo at week eight end point (all P<0.0001). The proportion of patients achieving a successful response to treatment at week eight was significantly higher with the combination of aliskiren and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo			mm Hg), change in 24-hr ABPM, change in biomarkers, safety	valsartan (66%) than with aliskiren alone (53%; P=0.0003) or valsartan alone (55%; P=0.0010). All active treatments were associated with significantly greater responder rates than placebo (30%; P<0.0001 for all). The proportion of patients achieving blood pressure control was significantly greater in the combination group (49%) than in the aliskiren (37%; P=0.0005) or valsartan (34%; P<0.0001) monotherapy groups. All active treatments were associated with significantly greater control rates than placebo (16%; P<0.0001 for all). The combination of aliskiren and valsartan was significantly more effective in lowering mean 24-hr ambulatory SBP and DBP than was either agent alone (P<0.0001 for all). The greater reductions in ambulatory blood pressure with aliskiren plus valsartan were maintained throughout the entire 24-hour dosing interval. Aliskiren and valsartan (P<0.0001) and monotherapy with aliskiren (P<0.0001) or valsartan (P=0.0002) provided significant increases in plasma renin concentrations versus placebo. Increases in plasma renin concentrations were significantly greater for the combination than aliskiren (P=0.0014) or valsartan (P<0.0001) monotherapy. Valsartan monotherapy produced significantly greater increases in plasma renin activity than placebo (160 vs 18%; P=0.0003). By contrast, aliskiren alone significantly reduced plasma renin activity by 73% (P<0.0001 vs placebo), while the combination of aliskiren plus valsartan led to a reduction in plasma renin activity of 44% (P<0.0001 vs placebo). The combination of aliskiren and valsartan (-31%; P<0.0001) and valsartan monotherapy (-25%; P=0.0007) provided significantly greater reductions in plasma aldosterone concentration than did placebo (7%), while aliskiren monotherapy had no significant effect (-5.9%; P=0.1059). Rates of adverse events and laboratory abnormalities were similar in all groups.
Yarows et al.[139] (2008)	Post-hoc analysis of patients with stage 2	N=1,797	Primary: Change in mean	Primary: In patients with stage 2 HTN, significantly greater reductions in DBP were

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Aliskiren 150 mg QD for 4 weeks, followed by 300 mg QD for 4 weeks vs valsartan 160 mg QD for 4 weeks, followed by 320 mg QD for 4 weeks vs aliskiren and valsartan 150-160 mg QD for 4 weeks, followed by 300-320 mg QD for 4 weeks (fixed-dose combination products) vs placebo	HTN from Oparil et al. Men and women ≥18 years of age with stage 1 to 2 essential HTN (mean sitting DBP 95 to 109 mm Hg and 8-hour ambulatory DBP ≥90 mm Hg)	8 weeks	sitting DBP Secondary: Change in mean sitting SBP, proportion of patients achieving a successful response to treatment (mean sitting DBP <90 mm Hg and/or ≥10 mm Hg reduction from baseline) or achieving blood pressure control (mean sitting SBP/DBP <140/90 mm Hg)	demonstrated in the aliskiren and valsartan 300-320 mg group compared to either higher-dose monotherapy group (P<0.05) and placebo (P<0.0001). Secondary: In patients with stage 2 HTN, significantly greater reductions in SBP were demonstrated in the aliskiren and valsartan 300-320 mg group compared to either higher-dose monotherapy group (P<0.05) and placebo (P<0.0001). DBP and SBP reductions in both monotherapy groups were significantly greater compared to placebo (P<0.0001). The proportion of patients with stage 2 HTN achieving blood pressure control at week eight was significantly greater in the aliskiren and valsartan 300-320 mg group compared to both monotherapy groups and placebo (P≤0.044). Blood pressure control rates in the aliskiren group were significantly greater than placebo (P<0.001). No significant difference was observed between the valsartan monotherapy and placebo groups.
Pool et al.[140] (2007) Aliskiren 75 to 300 mg QD vs	DB, MC, PC, PG, RCT Men and women ≥18 years with mild-to-moderate essential HTN	N=1,123 8 weeks	Primary: Change in mean sitting DBP Secondary: Change in mean sitting SBP, safety	Primary: Aliskiren 300 mg significantly (P<0.0001) lowered mean sitting DBP compared with placebo. Reductions in mean sitting DBP for aliskiren 75 and 150 mg compared to placebo failed to reach statistical significance (P=0.052 and P=0.051, respectively). Secondary:

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valsartan 80 to 320 mg vs aliskiren 75 to 300 mg and valsartan 80 to 320 mg vs valsartan and HCTZ 160-12.5 mg QD (fixed-dose combination) vs placebo	(mean sitting DBP ≥95 mm Hg after a 3- to 4-week single-blind placebo run-in period)			Aliskiren 300 mg significantly (P<0.0001) lowered mean sitting SBP compared with placebo. A statistically significant linear dose relationship was observed for the effect of aliskiren (75 to 300 mg) on mean sitting DBP (P=0.0002) and mean sitting SBP (P=0.0005). The effects of aliskiren monotherapy on mean sitting DBP and SBP across the 75 to 300 mg dose range were similar to the effects of valsartan 80 to 320 mg. Coadministration of aliskiren and valsartan produced a greater antihypertensive effect than either drug alone. Reductions in mean sitting DBP and SBP obtained with aliskiren 150 mg plus valsartan 160 mg and aliskiren 300 mg plus valsartan 320 mg were not significantly different from those observed with valsartan 160 mg plus HCTZ 12.5 mg. Responder rates were significantly greater than placebo for all 3 aliskiren monotherapy groups and for all aliskiren plus valsartan combinations. The proportion of responders with aliskiren 75 mg plus valsartan 80 mg was significantly greater than either component monotherapy (P<0.05). There was no significant difference between the proportion of responders to aliskiren 150 mg plus valsartan 160 mg or aliskiren 300 mg plus valsartan 320 mg compared with valsartan 160 mg plus HCTZ 12.5 mg. Control rates were higher with aliskiren 300 mg compared with placebo and with valsartan 160 mg plus HCTZ 12.5 mg compared with aliskiren 150 mg plus valsartan 160 mg, but there were no significant differences between aliskiren plus valsartan combinations and the respective monotherapies. Aliskiren and valsartan were generally well tolerated either as monotherapy or in combination. The overall incidence of adverse events and rate of discontinuations because of adverse events were similar to placebo in all active treatment groups.
Geiger et al.[141] (2009) Aliskiren 150 to 300 mg QD, added to existing HCTZ	AC, DB, RCT Patients ≥18 years of age with mild to moderate essential HTN who were	N=641 8 weeks	Primary: Change in DBP at week 8 Secondary: Change SBP at	Primary: After eight weeks of therapy, the triple therapy showed significantly greater reductions in SBP and DBP compared with the other groups. The additional SBP and DBP reductions were 7 and 5 mm Hg, respectively compared to aliskiren and HCTZ (P<0.0001), 3 and 2 mm Hg compared to valsartan and HCTZ (P<0.01), and 15 and 10 mm Hg compared to HCTZ monotherapy

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therapy vs valsartan 160 to 320 mg QD, added to existing HCTZ therapy vs aliskiren 150 to 300 mg and valsartan 160 to 320 mg QD, added to existing HCTZ therapy vs HCTZ 25 mg QD	taking HCTZ for 4 weeks with a DBP ≥95 mm Hg		week 8, change in DBP and SBP at week 4, proportion of patients achieving blood pressure control (SBP/DBP <140/90 mm Hg), change in plasma renin activity, plasma renin concentration	(P<0.001). Aliskiren and HCTZ and valsartan and HCTZ combination therapies were more effective compared to HCTZ monotherapy. Valsartan and HCTZ were more effective than aliskiren and HCTZ. SBP and DBP were reduced by 15 and 11 mm Hg, respectively in the aliskiren and HCTZ group. SBP and DBP were reduced by 18 and 14 mm Hg, respectively, in the valsartan and HCTZ group. Secondary: Blood pressure control rate was significantly higher with triple therapy compared to aliskiren and HCTZ (40.9%, P<0.001), valsartan and HCTZ (48.7%, P<0.001), and HCTZ monotherapy (20.5%, P<0.001). At week four, a significantly greater blood pressure control rate was observed for the triple therapy group at lower doses (150-160-25 mg) compared to the respective doses of the other groups: aliskiren and valsartan and HCTZ (300-320-25 mg) group (56%) compared to aliskiren and HCTZ (36.6%, P<0.05), valsartan and HCTZ (42.2%, P<0.05), and HCTZ monotherapy (19.9%, P<0.01). At week eight, plasma renin concentration was unchanged in the HCTZ group, but was significantly increased in other groups. A significant decrease in plasma renin activity from baseline was observed in the aliskiren and HCTZ group (P<0.001) and a significant increase was observed in the valsartan and HCTZ (P<0.001). In the HCTZ and triple therapy groups, there was no change in plasma renin activity (both P>0.75).
Maciejewski et al.[142] (2006) Valsartan 80 to 160 mg QD vs amlodipine 5 to 10	DB, PRO, RCT, XO African-Americans, older than 35 years, with baseline blood pressure >140/90 mm Hg and not on antihypertensive treatment	N=20 8 to 10 weeks for each arm with 2 week washout period before crossover	Primary: Comparison of 24 hour ABPM recordings Secondary: Magnitude of change from baseline in SBP and DBP with each	Primary: There was no difference between the groups based on 24 hour ABPM: SBP amlodipine 130±8 vs valsartan 127±17 (P=0.350) and DBP amlodipine 82±5 vs valsartan 84±16 (P=0.430). Secondary: There was no difference between groups in magnitude of change from baseline in blood pressure (amlodipine -25±8/-18±7 vs valsartan -25±9/-16±7; P=0.61), and in percent of patients achieving goal blood pressure, 70% in the valsartan group and 75% in the amlodipine group (P=0.62).

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mg QD If blood pressure exceeded 140/90 while on highest treatment dose, HCTZ 12.5mg/day was added to the regimen.			treatment, percent of patients who achieved goal <140/<90 with each treatment based on clinic blood pressure measurements	
Ichihara et al.[143] (2006) Valsartan 40 to 160 mg QD vs amlodipine 2.5 to 10 mg QD	RCT Patients with untreated HTN (clinic SBP >140 mm Hg and/or DBP >90 mm Hg; or ABPM SBP >135 mm Hg and/or DBP >98 mm Hg)	N=100 12 months	Primary: ABPM and clinic blood pressure Secondary: Pulse wave velocity, carotid intima-media thickness, urinary albumin excretion	Primary: Both treatments resulted in significant decreases in blood pressure, both ambulatory and clinic, over 12 months from baseline; blood pressure decreases were similar between treatment groups (between treatments: clinic SBP P=0.34; clinic DBP P=0.85; 24 hour ABPM P=0.14). Blood pressure variability decreased significantly in the amlodipine group compared to the valsartan group, where there was no change in blood pressure variability (P<0.01). Secondary: The decrease in pulse wave velocity was significant from baseline for both groups, but not significantly different from each other (P<0.05 from baseline). Intima-media thickness was not changed significantly from baseline for either treatment (P>0.05 for both from baseline). Urinary albumin excretion in the valsartan group decreased significantly both from baseline and compared to amlodipine treatment (P<0.05 from baseline, P value for comparison not reported).
Flynn et al.[144] (2008) <u>Phase 1</u> Valsartan low, medium or high dose (5 mg, 20 mg and 40 mg for <18	DB, MC, RCT Children one to five years of age with SBP ≥95th percentile for age, gender and height with minimum weight of	N=90 4 weeks (2 weeks of phase 1 and 2 weeks of phase 2)	Primary: Change in mean seated SBP from baseline to end of phase 1 and from end of phase 1 to the end of phase 2	Primary: In phase 1, valsartan significantly lowered SBP in all of the dose groups (SBP: low dose: -8.4 mm Hg; medium dose: -8.3 mm Hg; high dose: -8.6 mm Hg). From the end of phase 1 to the end of phase 2, subjects who remained on valsartan exhibited a mean reduction in seated SBP of -1.5 mm Hg, whereas placebo recipients had a mean increase in SBP of 1.5 mm Hg. The least-squares mean difference in the change in SBP between the pooled valsartan and placebo groups (-3.9 mm Hg) was significant (P=0.02).

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kg and 10 mg, 40 mg and 80 mg for ≥18 kg, respectively) QD Phase 2 Continue phase 1 valsartan dose vs placebo	8 kg; could have either untreated hypertension or inadequately controlled hypertension on current treatment		Secondary: Change in mean seated DBP from baseline to the end of phase 1 and change in mean seated DBP from the end of phase 1 to the end of phase 2	Secondary: In phase 1, valsartan significantly lowered DBP in all of the dose groups (low dose: -5.5 mm Hg; medium dose: -6.4 mm Hg; high dose: -5.5 mm Hg). From the end of phase 1 to the end of phase 2, a mean decrease in seated DBP was observed in the valsartan group (-2.5 mm Hg), whereas an increase of 2.0 mm Hg was observed in the placebo group. The least-squares mean difference in the change in DBP between the 2 pooled groups (-3.7 mm Hg) was significant (P=0.009).
Schaefer et al.[145] (2013) Phase 1 Valsartan low (0.25 mg/kg), medium (1 mg/kg) and high (4 mg/kg) dose QD Phase 2 Continue phase 1 valsartan dose vs placebo	DB, MC, PG, RCT Children six months to five years of age (weight 6 to 40 kg) with a documented history of hypertension (mean sitting SBP of ≥95th percentile for age, sex, and height)	N=75 8 weeks (6 weeks of phase 1 and 2 weeks of phase 2)	Primary: Mean sitting SBP reduction over first 6 weeks Secondary: Mean sitting DBP reduction over first 6 weeks and change from end of phase 1 to end of phase 2 for mean sitting SBP and DBP	Primary: At the end of phase 1 (six weeks), statistically significant reductions (P<0.05) from baseline in mean sitting SBP were observed for all the three doses (-8.3 mmHg for low dose, -10.3 mmHg for medium dose and -14.4 mmHg for high dose) of valsartan. Secondary: Statistically significant reductions (P <0.05) from baseline in mean sitting DBP were observed for all the three doses of valsartan after the first six weeks as well. During phase 2, an increase in mean sitting SBP was observed in both treatment groups. Least squares mean changes in SBP did not show any significant difference between pooled valsartan and placebo groups (LSM difference, 0.6; P=0.76). Small increases in mean sitting DBP from the end of phase 1 were observed in both treatment groups; the change being greater in the placebo group, but the difference between treatments was not statistically significant (LSM difference, -0.4; P=0.85).
Jankauskiene et al.[146] (2021) Valsartan 0.25 mg/kg/day	DB, MC, RCT Children one to five years of age with hypertension (mean SBP ≥95th percentile) with or	N=120 6 weeks	Primary: Change in mean SBP from baseline to 6 weeks Secondary: Change in mean	Primary: A clinically and statistically significant reduction in mean SBP from baseline to Week 6 was observed with the valsartan 4 mg/kg group compared with the valsartan 0.25 mg/kg group (8.5 vs 4.1 mmHg; P=0.0157). A positive dose-response relationship for mean SBP reduction was observed between the 0.25 mg/kg and 4 mg/kg groups (P=0.0012).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs valsartan 4 mg/kg/day	without CKD		SBP from baseline to 6 weeks in patients with or without CKD groupsops, safety	Secondary: In the CKD subgroup, a significant reduction in mean SBP was observed with 4 mg/kg (9.2 mmHg) versus 0.25 mg/kg (1.2 mmHg; P=0.0096). In the non-CKD subgroup, a numerically greater decrease in mean SBP was observed with 4 mg/kg (7.8 mmHg) versus 0.25 mg/kg (6.9 mmHg; P=0.6531). Incidence of adverse events was lower with valsartan 4 mg/kg than 0.25 mg/kg (41.9% vs 51.6%) and similar between CKD and non-CKD subgroups (48.4% vs 45.3%) irrespective of dose. Increase in serum potassium (>20% compared to baseline) was observed more frequently in patients with CKD compared to non-CKD patients.
Philipp et al.[147] (2007) <u>Study 1</u> Valsartan 40 to 320 mg QD and amlodipine 2.5 to 5 mg QD vs amlodipine 2.5 to 5 mg QD vs valsartan 40 to 320 mg QD vs placebo	DB, MC, PC, RCT Males and females, ages 18 years and older with HTN (mean sitting DBP ≥95 mm Hg and <110 mm Hg)	N=1,911 8 weeks	Primary: Mean sitting DBP Secondary: Change in mean sitting SBP, response rate (proportion of patients with mean sitting DBP <90 mm Hg or a ≥10 mm Hg reduction from baseline), control rate (proportion of patients with mean sitting DBP <90 mm Hg), adverse events (combined with study 2)	Primary: All treatments significantly decreased mean sitting DBP from baseline (P<0.05). Combination treatment resulted in significantly greater blood pressure reduction than either monotherapy (P<0.05 for all combinations compared to respective doses of monotherapy except amlodipine 2.5 mg and valsartan 40 mg QD). Secondary: All treatments significantly decreased mean sitting SBP from baseline (P<0.05). Combination treatment resulted in significantly greater blood pressure reduction than either monotherapy (P<0.05 for all combinations compared to respective doses of monotherapy). Response rates were significantly different from placebo for all treatment groups (P<0.05). Response rates for combination products were significantly different than each monotherapy for the following combinations: amlodipine 5 mg plus valsartan 80 mg, amlodipine 5 mg plus valsartan 40 mg and amlodipine 2.5 mg plus valsartan 80 mg (P<0.05 for each combination compared to both monotherapy).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Response rates for all combinations produced significantly improved compared to either one of the monotherapies except amlodipine 2.5 mg plus valsartan 40 mg (P<0.05 for each combination compared to one of the respective monotherapy). Control rates with therapy were significantly better than placebo, with the highest control rate achieved with amlodipine 5 mg plus valsartan 320 mg (P<0.05 compared to placebo, P value not reported for others). Adverse event rates were not significantly different among combination treatment, amlodipine treatment, and placebo. Adverse event rates were significantly different between amlodipine plus valsartan and valsartan monotherapy (P<0.05). The most commonly reported adverse events for combination treatment were: peripheral edema, headache, nasopharyngitis, upper respiratory tract infection and dizziness. Peripheral edema occurred significantly less frequently in the combination treatment group than the amlodipine monotherapy group (5.4 vs 8.7%; P=0.014) and significantly more frequently than in the valsartan monotherapy group (5.4 vs 2.1%; P<0.001). Peripheral edema occurrence in the valsartan group was similar to the rate in the placebo group.
Philipp et al.[147] (2007) <u>Study 2</u> Valsartan 160 or 320 mg QD and amlodipine 10 mg QD vs amlodipine 10 mg QD vs	DB, MC, PC, RCT Male and females, ages 18 years and older with hypertension (mean sitting DBP ≥95 mm Hg and <110 mm Hg)	N=1,250 8 weeks	Primary: Mean sitting DBP Secondary: Change in mean sitting SBP, response rate (proportion of patients with mean sitting DBP <90 mm Hg or a ≥10 mm Hg reduction from baseline), control rate (proportion of	Primary: Mean sitting DBP was significantly reduced for both combination as compared to the individual components and to placebo (P<0.05). Secondary: Response rates and control rates for combination treatments were significantly greater than valsartan monotherapy therapy and placebo therapy, but not different from amlodipine monotherapy (P<0.05). Adverse event rates were not significantly different between combination treatment, amlodipine treatment and placebo. Adverse event rates were significantly different between amlodipine plus valsartan and valsartan monotherapy (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
valsartan 160 to 320 mg QD vs placebo			patients with mean sitting DBP <90 mm Hg), adverse events (combined with study 1)	
Sinkiewicz et al.[148] (2009) Amlodipine and valsartan 10-160 mg or 5-160 mg QD (fixed-dose combination product) vs valsartan 160 mg QD	AC, DB, MC, RCT Patients ≥18 years of age with essential HTN (mean sitting DBP ≥90 mm Hg and <110 mm Hg) who were inadequately controlled on valsartan 160 mg	N=947 8 weeks	Primary: Change from baseline in mean DBP Secondary: Change from baseline in mean sitting SBP, responder rate (mean DBP <90 mm Hg or ≥10 mm Hg reduction from baseline), and DBP control rate (mean DBP < 90 mm Hg)	Primary: At week eight, a significantly greater reduction in mean DBP was observed with both amlodipine and valsartan combinations (10-160 mg: -11.5 mm Hg, 5-160 mg: -9.6 mm Hg; P<0.0001 for both) compared to valsartan monotherapy (-6.7 mm Hg). Secondary: At week eight, a significantly greater reduction in mean SBP was observed in both amlodipine and valsartan combinations (10-160 mg: -14.3 mm Hg, 5-160 mg: -12.2 mm Hg; P<0.0001 for both) compared to valsartan monotherapy (-8.3 mm Hg). Overall mean SBP/DBP reductions of 22.5/15.5 and 21.3/13.7 mm Hg were observed in the amlodipine and valsartan 10-160 and 5-160 mg treatment groups, respectively compared to 16.7/11.4 mm Hg in the valsartan 160 mg group. The amlodipine and valsartan 10-160 mg combination showed a significantly greater reduction in mean SBP/DBP compared to amlodipine and valsartan 5-160 mg (P<0.001). Responder rates were higher in both amlodipine and valsartan groups (10-160 mg: 81% [P<0.0001]; 5-160 mg: 68% [P=0.0018], respectively) compared to valsartan monotherapy (57%). Peripheral edema was the most frequent adverse event, which was reported in 9.1% of patients receiving amlodipine and valsartan (10-160 mg), 0.9% of patients receiving amlodipine and valsartan (5-160 mg), and 1.3% of patients receiving valsartan monotherapy.
Philipp et al (abstract).[149] (2011)	Post-hoc analysis Patients with HTN	N=834 Not reported	Primary: Rate of blood pressure control	Primary: Two weeks after starting therapy, blood pressure control rates were greater with amlodipine and valsartan 10-320 mg/day (49%) vs monotherapies (32 to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Amlodipine and valsartan 10-160 or 10-320 mg/day (fixed-dose combination product) vs amlodipine 10 mg/day vs valsartan 160 or 320 mg/day vs placebo			(<140/90 mm Hg), change in baseline blood pressure Secondary: Safety	38%) and placebo (16%). Consistent results were observed in patients with stage 1 and 2 HTN. Among patients receiving combination therapy, statistically significant differences were observed at endpoint vs comparators. At all baseline blood pressure levels, the probability of achieving a blood pressure <140/90 or <130/80 mm Hg was greater with combination therapy compared to monotherapies and placebo. Secondary: Overall adverse events incidence was similar with combination therapy vs monotherapies and placebo.
Fogari et al.[150] (2009) Valsartan and amlodipine 160-5 to 10 mg/day (fixed-dose combination) vs irbesartan and HCTZ 300-12.5 to 25 mg/day (fixed-dose combination product)	Blind end endpoint, OL, PG, PRO, RCT Patients 75 to 89 years of age with moderate essential HTN (SBP ≥160, DBP >95 to <110 mm Hg)	N=94 24 weeks	Primary: Proportion of patients achieving DBP <90 mm Hg Secondary: Changes in ambulatory blood pressure, lying and standing changes in blood pressure, safety	Primary: The proportion of patients receiving valsartan and amlodipine and irbesartan and HCTZ who achieved blood pressure <140/<90 mm Hg was 82.9 and 85.1% (P value not significant between groups). Secondary: Both treatment combinations resulted in a significant decrease in ambulatory blood pressure without any differences between treatment groups (P<0.001 from baseline, P>0.05 between groups). Results were similar between groups for lying SBP/DBP but patients receiving irbesartan and HCTZ experienced greater changes in ambulatory blood pressure than those receiving valsartan and amlodipine (17.2/9.0 vs 10.1/1.9 mm Hg; P<0.05 for SBP and P<0.01 for DBP). Changes from baseline in serum potassium (decrease) and uric acid (increase)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				were significant for those receiving irbesartan and HCTZ, but not valsartan and amlodipine (P<0.05 for irbesartan and HCTZ).
Poldermans et al.[151] (2007) Valsartan 160 mg QD and amlodipine 5 to 10 mg QD vs lisinopril 10 to 20 mg and HCTZ 12.5 mg QD	AC, DB, MC, PG, RCT Males and females, ages 18 years and older with HTN (mean DBP ≥110 mm Hg and <120 mm Hg)	N=130 6 weeks	Primary: Safety/adverse events, vital signs, hematology, biochemistry variables Secondary: Efficacy (mean DBP, response rate, proportion of patients with mean DBP <90 mm Hg or a ≥10 mm Hg reduction from baseline)	Primary: Both treatments were well tolerated, 26 (40.6%) of patients receiving amlodipine and valsartan and 21 (31.8%) of patients receiving lisinopril and HCTZ reported an adverse events and most were not considered drug related. Peripheral edema was reported more often in the amlodipine and valsartan group than the lisinopril and HCTZ group (7.7 vs 1.5%) and cough was reported less often in the amlodipine and valsartan group than the receiving lisinopril and hydrochlorothiazide group (1.6 vs 3.0%). No difference was found between the treatments in changes in laboratory values or biochemistry variables. Secondary: Both treatments led to a reduction in mean SBP and DBP (P<0.0001 for both from baseline) but were not significantly different from each other. Mean blood pressure for each group at study end: amlodipine and valsartan 135.0/83.6 mm Hg and lisinopril and HCTZ 138.7/85.2 mm Hg. The response rate was similar among the groups (100 vs 95.5%; P value not significant).
White et al.[152] (2008) Val-DICTATE Valsartan and HCTZ 160-12.5 mg QD (fixed-dose combination product) vs HCTZ 25 mg QD	AC, MC, PG, RCT Patients with stage 1 to 2 HTN whose BP remained uncontrolled on HCTZ 12.5 mg	4 weeks Duration not reported	Primary: Percentage of patients whose clinic blood pressure values were <140/90 mm Hg and blood pressure values Secondary: Not reported	Primary: A significantly higher proportion of hypertensive patients met blood pressure control levels in the valsartan and HCTZ group (37%) compared to the HCTZ group (16%; P<0.001). Changes in SBP and DBP were significantly greater with valsartan and HCTZ (-12. 4/-7.5 mm Hg) compared to HCTZ (-5.6/-2.1 mm Hg; P<0.001). Secondary: Not reported
Waeber et al.[153]	OL, RCT	N=327	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2001) Valsartan 80 mg QD, which was switched to valsartan 80 mg and HCTZ 12.5 mg QD or valsartan 80 mg and benazepril 10 mg QD	Patients with mild-to-moderate uncontrolled HTN (DBP ≥90) while on valsartan monotherapy	4 weeks	Efficacy and safety Secondary: Not reported	The two combinations produced an additional blood pressure reduction compared to monotherapy (P<0.001 for both), with similar DBP reductions reported for the two combination groups (-4.5 mm Hg with valsartan plus HCTZ and -3.3 mm Hg with valsartan plus benazepril). SBP reductions of -6.7 and -3.2 mm Hg with valsartan plus HCTZ and valsartan plus benazepril, respectively, were reported (P=0.1). At the end of the trial, the blood pressure of the responders to valsartan monotherapy was lower than that of patients requiring combination therapy. Valsartan given alone or in association with HCTZ or benazepril was well tolerated. Secondary: Not reported
Schweizer et al.[154] (2007) Valsartan and HCTZ 160-25 mg QD (fixed-dose combination)	OL Hypertensive patients not adequately controlled by free combination of candesartan and HCTZ for 4 weeks	N=197 8 weeks	Primary: Reduction in mean sitting DBP between week 4 and 8 Secondary: Reduction in mean sitting SBP from week 4 to 8	Primary: At baseline, DBP was 103.0 mm Hg. After four weeks of candesartan and HCTZ, DBP decreased to 93.8 mm Hg. Subsequent treatment with valsartan and HCTZ for four additional weeks reduced DBP to 88.7 mm Hg. This represented an additional decrease in DBP of 5.1 mm Hg (P<0.0001). Secondary: The valsartan and HCTZ fixed-dose combination reduced SBP by 3.4 mm Hg (P=0.0029).
Lai et al.[155] (2011) Valsartan and HCTZ 80-12.5 mg QD (fixed-dose combination product)	MC, OS Asian patients with stage 1 or 2 essential HTN	N=7,567 24 week (follow-up)	Primary: Safety, efficacy Secondary: Not reported	Primary: After 24 weeks, basal blood pressure was 155.9±13.3/96.3±10.1 mm Hg. SBP and DBP reductions were -25.4±15.2 and -14.9±13.5 mm Hg (P<0.001). Response and control rates increased continuously from baseline to trial end (trial end: 94.3 and 73.6%, respectively). Based on a four point global assessment scale, 96.8% of patients and physicians reported good, very good, or excellent for subjective efficacy and tolerability assessments. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Izzo Jr et al.[156] (2011) ValVET Valsartan and HCTZ 160-12.5 mg QD (fixed-does combination product) vs valsartan 160 mg QD vs HCTZ 12.5 mg QD All patients were allowed to up titrate study medication if blood pressure did not improve.	DB, RCT Patients ≥70 years of age with systolic HTN	N=384 16 weeks	Primary: Change in baseline SBP at week 4 Secondary: Time to blood pressure control	Primary: At week four, reductions in baseline SBP were significantly greater with combination therapy (-17.3 mm Hg) compared to valsartan (-8.6 mm Hg; P<0.001). At this time, reductions with combination therapy and HCTZ were similar (-17.3 vs -13.6 mm Hg; P=0.096). Secondary: Median time to blood pressure control was significantly shorter with combination therapy compared to HCTZ (four vs eight weeks; P<0.05) and valsartan (four vs 12 weeks; P<0.0001).
Duprez et al.[157] (abstract) (2011) ValVET Valsartan and HCTZ 160-12.5 mg QD (fixed-does combination product)	Subgroup analysis Patients ≥70 years of age with systolic HTN	N=108 Duration not specified	Primary: Change in ambulatory SBP Secondary: Safety	Primary: Initiation of treatment with combination valsartan and HCTZ reduced ambulatory blood pressure more effectively compared to monotherapy with either valsartan or HCTZ throughout daytime, night-time, and 24 hr monitoring periods, as well as during the last four to six hour dosing periods. Twenty-four hour ambulatory blood pressure was reduced from 141.1/76.5 to 125.8/69.2 mm Hg by week four with combination valsartan and HCTZ compared to reductions from 142.2/78.7 to 139.1/77.5 mm Hg with HCTZ and 142.2/78.3 to 136.4/75.1 mm Hg with valsartan (P<0.01 for all).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs valsartan 160 mg QD vs HCTZ 12.5 mg QD All patients were allowed to up titrate study medication if blood pressure did not improve.				Secondary: In the overall study, tolerability was similar among the three treatment groups.
Fogari et al.[158] (2006) Valsartan 160 mg vs olmesartan 20 mg All patients were also receiving HCTZ 12.5 mg QD.	PG, PRO, RCT Hypertensive patients aged 35 to 75 years with DBP 90 to 110 mm Hg after 4 weeks of monotherapy on either valsartan or olmesartan	N=130 8 weeks (4 weeks of combination therapy)	Primary: Changes in blood pressure Secondary: Not reported	Primary: Both combinations induced a greater ambulatory blood pressure reduction than monotherapy. However, mean reduction from baseline in the valsartan and HCTZ-treated patients (-21.5/-14.6 mm Hg for 24 hours, -21.8/-14.9 mm Hg for daytime, and -20.4/-13.7 mm Hg for nighttime SBP/DBP) was greater than in the olmesartan and HCTZ-treated patients (-18.8/-12.3 mm Hg for 24 hours, -19.3/-12.8 mm Hg for daytime, and -17.4/-10.6 mm Hg for nighttime SBP/DBP). The difference between the effects of the two treatments was significant (P<0.01). Plasma concentrations of HCTZ were significantly greater with valsartan than with olmesartan at each determination time (P<0.05). Secondary: Not reported
White et al.[159] (2008) Valsartan 160 mg and HCTZ 25 mg	DB, PC, RCT Hypertensive patients	N=1,181 8 weeks	Primary: Changes in DBP and SBP at 8 weeks Secondary:	Primary: Changes from baseline in blood pressure following telmisartan and HCTZ (-24.6/-18.2 mm Hg) were significantly greater than both valsartan and HCTZ (-22.5/-17.0 mm Hg; P=0.017 for SBP and P=0.025 for DBP), and placebo (-4.1/-6.1 mm Hg; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD vs telmisartan 80 mg and HCTZ 25 mg QD vs placebo			Safety	Secondary: The total number of patients with at least one adverse event reported was similar among the 3 treatment groups and was 37% for valsartan and HCTZ, 36% for telmisartan and HCTZ, and 42% for placebo.
Sharma et al.[160] (2007) SMOOTH Valsartan 160 mg for 4 weeks vs telmisartan 80 mg for 4 weeks After 4 weeks, all patients received add-on HCTZ 12.5 mg QD for 6 six weeks.	MC, OL, PRO, RCT, blinded-end point Men and women aged ≥30 years with mild-to-moderate HTN (mean seated SBP 140 to 179 mm Hg and/or DBP 95 to 109 mm Hg), with type 2 diabetes and BMI >27 kg/m^2	N=840 10 weeks	Primary: Change in mean ambulatory SBP and DBP Secondary: Not reported	Primary: At 10 weeks, telmisartan and HCTZ provided significantly greater reductions in the last six hours of mean ambulatory blood pressure (differences in SBP were 3.9 mm Hg; P<0.0001 and differences in DBP were 2.0 mm Hg; P=0.0007). Telmisartan and HCTZ also produced significantly greater reductions than valsartan and HCTZ in 24-hour mean ambulatory blood pressure (differences in SBP were 3.0 mm Hg; P=0.0002 and differences in DBP were 1.6 mm Hg; P=0.0006) and during morning, daytime and nighttime periods (P<0.003). Both treatments were well tolerated. Secondary: Not reported
Calhoun et al.[161] (2009) Valsartan and HCTZ 320-25 mg QD (fixed-dose combination product)	DB, MC, RCT Patients 18 to 85 years of age with moderate to severe essential HTN	N=2,271 8 weeks	Primary: Difference in mean sitting diastolic blood pressure and mean sitting systolic blood pressure Secondary: Not reported	Primary: At each assessment after week three, a significantly greater proportion of patients receiving triple therapy achieved overall blood pressure control (<140/90 mm Hg) compared to those receiving any of the dual therapies (all P<0.0001). At end point, 70.8% of patients in the triple-therapy group achieved control, compared to 48.3% for valsartan and HCTZ, 54.1% for amlodipine and valsartan, and 44.8% for amlodipine and HCTZ (all P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs amlodipine and valsartan 10-320 mg QD (fixed-dose combination product) vs amlodipine and HCTZ 10-25 mg QD (fixed-dose combination product) vs amlodipine and valsartan and HCTZ 10-320-25 mg QD (fixed-dose combination product)				Triple therapy with amlodipine and valsartan and HCTZ improved blood pressure control significantly better than any of the dual therapies. Secondary: Not reported
Calhoun et al.[162] (2009) Valsartan and HCTZ 320-25 mg QD (fixed-dose combination product) vs amlodipine and valsartan 10-320	Secondary analysis Patients 18 to 85 years of age with moderate to severe HTN (mean SBP/DBP ≥145/≥100 mm Hg)	N=2,271 8 weeks	Primary: Proportion and mean SBP of patients with mean SBP reductions ≥60, ≥50, ≥40, ≥30 and ≥20 mm Hg at week three and at the end of the study Secondary: Changes from baseline in mean	Primary: The proportion of patients with mean SBP reductions ≥20 mm Hg was greater with triple therapy than dual therapy at week three (74.5 vs 58.8 to 65.5%) and at study endpoint (87.6 vs 75.8 to 81.5%). More patients who received triple therapy, as compared to dual therapy, achieved mean SBP reductions of ≥30, ≥40, ≥50 and ≥60 mm Hg at week three and at study endpoint (P value not reported). In patients with severe SBP (≥180 mm Hg), triple therapy resulted in significantly greater reductions than those for each dual therapy at week three (P<0.01), except for amlodipine/valsartan (P=0.11).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg QD (fixed-dose combination product) vs amlodipine and HCTZ 10-25 mg QD (fixed-dose combination product) vs amlodipine and valsartan and HCTZ 10-320-25 mg QD (fixed-dose combination product)			SBP based upon baseline severity, SBP control rates, safety	Secondary: Patients with higher baseline mean SBP had greater reductions in mean SBP than those with lower baseline mean SBP. Changes in mean SBP were significantly greater for triple therapy than dual therapy for all baseline SBP (P<0.05), except for valsartan and HCTZ and amlodipine and HCTZ in patients with baseline mean SBP 150 to <160 mm Hg (P value not reported). Significantly more patients (91.8%) receiving triple therapy achieved SBP control (≥20 mm Hg reduction or mean SBP <140 mm Hg) compared to those receiving amlodipine and HCTZ (80.1%), valsartan and HCTZ (80.8%) or valsartan and amlodipine (85.7%) (P<0.01 for all). The overall incidence of adverse events was comparable across treatments, regardless of baseline blood pressure severity.
Karotsis et al.[163] (2006) Valsartan 80 mg QD vs lisinopril 10 mg QD vs chlorthalidone 12.5 mg QD vs	RCT Patients 25 to 79 years of age with uncontrolled HTN (average office blood pressure >140/90 mm Hg for all or >153/85 mm Hg for diabetics or patients <65 years of age, confirmed on 2 office visits ≥1 week apart) after ≥4 weeks of OL monotherapy with diltiazem at 240 mg	N=211 8 weeks	Primary: Blood pressure Secondary: Not reported	Primary: There was a significant decline in both office and home SBP and DBP during the trial with all treatments. The antihypertensive effect was more pronounced and reached significance when home blood pressure monitoring was used in comparison to office blood pressure without the white-coat effect (P<0.001 for all blood pressure changes). With or without the white-coat effect, blood pressure still declined and the differences were significant (P<0.0001 for all blood pressure changes). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
felodipine 5 mg QD All patients also received diltiazem 240 mg QD.	QD			
Conlin et al.[164] (2000) PREVAIL Candesartan 8 to 16 mg QD, irbesartan 150 to 300 mg QD, losartan 50 to 100 mg QD, and valsartan 80 to 160 mg QD vs another ARB vs ARB plus low-dose HCTZ	MA Patients with HTN	N=11,281 (43 trials) Duration varied	Primary: Weighted average for SBP and DBP reduction with ARB monotherapy, dose titration, and with the addition of low-dose HCTZ were calculated; responder rates Secondary: Not reported	Primary: The absolute weighted-average reductions in DBP (8.2 to 8.9 mm Hg) and SBP (10.4 to 11.8 mm Hg) for ARB monotherapy were comparable for all ARBs. Responder rates for ARB monotherapy were 48 to 55%. Dose titration resulted in slightly greater blood pressure reductions and an increase in responder rates of 53 to 63%. ARB and HCTZ combinations produced substantially greater reductions in SBP (16.1 to 20.6 mm Hg) and DBP (9.9 to 13.6 mm Hg) than ARB monotherapy. Responder rates for ARB and HCTZ combinations were 56 to 70%. The authors concluded that candesartan, irbesartan, losartan, and valsartan produced comparable antihypertensive efficacy when administered at their recommended doses, a near flat dose response when titrating from starting to maximum recommended dose, and substantial potentiation of the antihypertensive effect with addition of HCTZ. Secondary: Not reported
Stanton et al.[165] (2010) Aliskiren 300 mg QD vs irbesartan,	MA Adults with mild to moderate essential HTN	N=4,877 (8 trials) 4 to 12 weeks	Primary: Paradoxical blood pressure rises, as well as the percentage of patients with SBP increases (>10 or >20 mm Hg) or DBP increases (>5	Primary: There were no significant differences among the pooled aliskiren, irbesartan, losartan, valsartan, ramipril, and HCTZ groups in the incidence of SBP increases >10 mm Hg (P=0.30) and >20 mm Hg (P=0.28) or DBP increases >5 mm Hg (P=0.65) and >10 mm Hg (P=0.5). Increases in SBP and DBP occurred significantly more frequently in the pooled placebo group than the aliskiren group (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
losartan, valsartan, ramipril, HCTZ, placebo			or >10 mm Hg) from baseline Secondary: Not reported	Secondary: Not reported
Sundström et al.[166] (2023) Amlodipine 10 mg vs candesartan 16 mg vs lisinopril 20 mg vs HCTZ 25 mg Half doses given weeks 1 and 2 of each treatment period, and full doses weeks 3 through 9	DB, PRO, XO, RCT Patients aged 40 to 75 years previously diagnosed with HTN, with SBP 140 to 159 mmHg within a five-year period prior to the start of the trial and SBP 140 to 179 mm Hg and DBP ≤109 mm Hg at the randomization visit Patients were pharmacologically untreated or used BP-lowering monotherapy at the inclusion visit	N=280 Six treatment periods, each being 7 to 9 weeks in duration, after a 2 week washout period; 1-week washout periods between each treatment period	Primary: Ambulatory daytime SBP at the end of each treatment period Secondary: Not reported	Primary: Participants had higher BP when taking HCTZ than when taking other treatments, when taking amlodipine compared with lisinopril, and when taking candesartan compared with lisinopril The blood pressure response to different treatments varied considerably between individuals (P<0.001), specifically for the choices of lisinopril vs hydrochlorothiazide, lisinopril vs amlodipine, candesartan vs hydrochlorothiazide, and candesartan vs amlodipine. On average, personalized treatment had the potential to provide an additional 4.4 mm Hg–lower systolic blood pressure. Secondary: Not reported
Lindholm et al.[167] (2005) Other antihypertensive therapies (amiloride, amlodipine, bendro-	MA 13 RCTs evaluating the treatment of primary HTN with a β-blocker as first-line treatment (in ≥50% of all patients in one treatment	N=105,951 2.1 to 10.0 years	Primary: Stroke, MI, all-cause mortality Secondary: Not reported	Primary: The RR of stroke was 16% higher with β-blocker therapy than for the comparator therapies (RR, 1.16; 95% CI, 1.04 to 1.30; P=0.009). The RR of stroke was the highest with atenolol (26% higher) compared to other non β-blockers (RR, 1.26%; 95% CI, 15 to 38; P<0.0001). The relative risk of MI was 2% higher for β- blocker therapy than for the comparator therapies (RR, 1.02; 95% CI, 0.93 to 1.12), which was not significant (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
flumethiazide*, captopril, diltiazem, enalapril, felodipine, HCTZ, isradipine, lacidipine, lisinopril, losartan, or verapamil) or placebo vs β-blocker therapy (atenolol, metoprolol, oxprenolol*, pindolol, or propranolol)	group) and outcome data for all-cause mortality, cardiovascular morbidity or both			The RR of all-cause mortality was 3% higher for β-blocker therapy than for the comparator therapies (RR, 1.16; 95% CI, 0.99 to 1.08; P=0.14). Secondary: Not reported
Van Bortel et al.[168] (2008) ACE inhibitor, ARB, β-blocker, calcium channel blocker, or placebo vs nebivolol	MA 12 RCTs involving >25 patients with essential HTN where nebivolol 5 mg QD was compared to placebo or other active drugs for >1 month	N=2,653 Duration varied	Primary: Antihypertensive effect and tolerability Secondary: Not reported	Primary: Overall, higher response rates were observed with nebivolol than all other antihypertensive agents combined (OR, 1.41; 95% CI, 1.15 to 1.73; P=0.001) and compared to the ACE inhibitors (OR, 1.92; 1.30 to 2.85; P=0.001), but response rates to nebivolol were similar to β-blockers (OR, 1.29; 95% CI, 0.81 to 2.04; P=0.283), calcium channel blockers (OR, 1.19; 95% CI, 0.83 to 1.70; P=0.350) and losartan (OR, 1.35; 95% CI, 0.84 to 2.15; P=0.212). Overall, a higher percentage of patients obtained normalized blood pressure with nebivolol compared to the other antihypertensive agents combined (OR, 1.35; 95% CI, 1.07 to 1.72; P=0.012). A higher percentage of patient receiving nebivolol obtained normalized blood pressure compared to losartan (OR, 1.98; 95% CI, 1.24 to 3.15; P=0.004) and calcium channel blockers (OR, 1.96; 95% CI, 1.05 to 1.96; P=0.024), but not when compared to other β-blockers (OR, 1.29; 95% CI, 0.81 to 1.65; P=0.473).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Overall, the percentage of adverse events was significantly lower with nebivolol compared to the other antihypertensive agents combined (OR, 0.59; 95% CI, 0.48 to 0.72; P<0.001) and similar to placebo (OR, 1.16; 95% CI, 0.76 to 1.67; P=0.482). In comparing nebivolol to the individual treatments, nebivolol had a lower percentage of adverse events compared to losartan (OR, 0.52; 95% CI, 0.30 to 0.89; P=0.016), the other β-blockers (OR, 0.56; 95% CI, 0.36 to 0.85; P=0.007) and calcium channel blockers (OR, 0.49; 95% CI 0.33 to 0.72; P<0.001), but was similar to ACE inhibitors (OR, 0.75; 95% CI 0.52 to 1.08). Secondary: Not reported
Wiysonge et al.[169] (2007) Other antihypertensive therapies (i.e., placebo, diuretics, calcium channel blockers, or renin-angiotensin system inhibitors) vs β-blockers (atenolol, metoprolol, oxprenolol*, or propranolol)	MA 13 RCTs evaluating patients ≥18 years of age with HTN	N=91,561 Duration varied	Primary: All-cause mortality Secondary: Stroke, CHD, cardiovascular death, total cardiovascular disease, adverse reactions	Primary: There was not a significant difference observed in all-cause mortality between β-blocker therapy and placebo (RR, 0.99; 95% CI, 0.88 to 1.11; P value not reported), diuretics (RR, 1.04; 95% CI, 0.91 to 1.19; P value not reported) or renin-angiotensin system inhibitors (RR, 1.10; 95% CI, 0.98 to 1.24; P value not reported). There was a significantly higher rate in all-cause mortality with β-blocker therapy compared to calcium channel blockers (RR, 1.07; 95% CI, 1.00 to 1.14; P=0.04). Secondary: There was a significant decrease in stroke observed with β-blocker therapy compared to placebo (RR, 0.80; 95% CI, 0.66 to 0.96). Also there was a significant increase in stroke with β-blocker therapy compared to calcium channel blockers (RR, 1.24; 95% CI, 1.11 to 1.40) and renin-angiotensin system inhibitors (RR, 1.30; 95% CI, 1.11 to 1.53), but there was no difference observed compared to diuretics (RR, 1.17; 95% CI, 0.65 to 2.09). CHD risk was not significantly different between β-blocker therapy and placebo (RR, 0.93; 95% CI, 0.81 to 1.07]), diuretics (RR, 1.12; 95% CI, 0.82 to 1.54), calcium channel blockers (RR, 1.05; 95% CI, 0.96 to 1.15) or renin-angiotensin system inhibitors (RR, 0.90; 95% CI, 0.76 to 1.06). The risk of total cardiovascular disease was lower with β-blocker therapy compared to placebo (RR, 0.88; 95% CI, 0.79 to 0.97). The effect of β-blocker

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				therapy on cardiovascular disease was significantly worse than that of calcium channel blockers (RR, 1.18; 95% CI, 1.08 to 1.29), but was not significantly different from that of diuretics (RR, 1.13; 95% CI, 0.99 to 1.28) or renin-angiotensin system inhibitors (RR, 1.00; 95% CI, 0.72 to 1.3). There was a significantly higher rate of discontinuation due to side effects with β-blocker therapy compared to diuretics (RR, 1.86; 95% CI, 1.39 to 2.50) and renin-angiotensin system inhibitors (RR, 1.41; 95% CI, 1.29 to 1.54), but there was no significant difference compared to calcium channel blockers (RR, 1.20; 95% CI, 0.71 to 2.04). Actual side effects were not reported.
Baguet et al.[170] (2007) Antihypertensive drugs (enalapril, ramipril, trandolapril, candesartan, irbesartan, losartan, olmesartan, telmisartan, valsartan, HCTZ, indapamide SR*, atenolol, amlodipine, lercanidipine*, manidipine*, enalapril, ramipril, trandolapril, and aliskiren) Drugs were used as monotherapy, either at a fixed daily dosage or in increasing	MA Patients greater than 18 years of age with mild or moderate essential HTN (SBP 140 to 179 mm Hg and/or DBP 90 to 109 mm Hg)	N=10,818 8 to 12 weeks	Primary: Weighted average reductions in SBP and DBP Secondary: Not reported	Primary: Data did not reflect outcomes from direct, head-to-head comparative trials or formal comparisons between drugs. Diuretics (-19.2 mm Hg; 95% CI, -20.3 to -18.0), calcium channel blockers (-16.4 mm Hg; 95% CI, -17.0 to -15.8) and ACE inhibitors (-15.6 mm Hg; 95% CI, -17.6 to -13.6) produced the greatest reductions in SBP from baseline (P values not reported). The magnitude of DBP reductions were generally similar among all drug classes; however, the greatest reductions in DBP from baseline were observed with the β-blocker, atenolol (-11.4 mm Hg; 95% CI, -12.0 to -10.9), calcium channel blockers (-11.4 mm Hg; 95% CI, -11.8 to -11.1) and diuretics (-11.1 mm Hg; 95% CI, -11.7 to -10.5) (P values were not reported). The weighted average reduction of SBP and DBP for each drug class were as follows: Diuretics: -19.2 (95% CI, -20.3 to -18.0) and -11.1 mm Hg (95% CI, -11.7 to -10.5), respectively. β-blockers: -14.8 (95% CI, -15.9 to -13.7) and -11.4 mm Hg (95% CI, -12.0 to -10.9), respectively. Calcium channel blockers: -16.4 (95% CI, -17.0 to -15.8) and -11.4 mm Hg (95% CI, -11.8 to -11.1), respectively. ACE inhibitors: -15.6 (95% CI, -17.6 to -13.6) and -10.8 mm Hg (95% CI, -11.9 to -9.7), respectively. ARBs: -13.2 (95% CI, -13.6 to -12.9) and -10.3 mm Hg (95% CI, -10.5 to -10.1), respectively. Renin inhibitor: -13.5 (95% CI, -14.2 to -12.9) and -11.3 mm Hg (95% CI, -11.7 to -10.9), respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dosages. Although cicletanine*, furosemide and spironolactone were considered for inclusion, none of the trials relating to these agents satisfied all inclusion criteria.				Secondary: Not reported
Miscellaneous				
Papademetriou et al.[171] (2004) SCOPE Candesartan 16 mg/day vs placebo in addition to conventional therapy (diuretics, ACE inhibitors, β-blockers, calcium channel blockers)	DB, MC, PC, PG, RCT Patients 7 to 89 years old with isolated systolic HTN (SBP >160 mm Hg and DBP <90 mm Hg) and MMSE scores ≥24	N=1,518 3.7 years	Primary: First major coronary event including cardiovascular death, nonfatal MI, or nonfatal stroke Secondary: cardiovascular death, nonfatal and fatal stroke and MI	Primary: There was no difference in the first major cardiovascular event between patients (with isolated systolic hypertension) who were treated with candesartan vs placebo (RR, 0.89; 95% CI, 0.65 to 1.21; P>0.20). Secondary: A total of 20 fatal/nonfatal strokes occurred in the candesartan group and 35 in the control group (RR, 0.58; 95% CI, 0.33 to 10) for a RR reduction of 42% (P=0.050 unadjusted and P=0.049 adjusted for baseline risk). There were no marked or statistically significant differences between the treatment groups in other cardiovascular end points or all-cause mortality.
Ogihara et al.[172] (2008) CASE-J Candesartan 4 to 12 mg QD vs	AC, MC, OL, RCT Patients with high risk HTN (SBP ≥140 mm Hg or DBP ≥90 mm Hg in patients <70 years old or SBP ≥160	N=4,703 Up to 4 years	Primary: First fatal or nonfatal cardiovascular event Secondary: All-cause death, new-onset diabetes,	Primary: A total of 134 patients experienced a cardiovascular event in each treatment regimen (HR, 10; 95% CI, 0.78 to 1.27; P=0.969). Secondary: All-cause death rates did not differ between treatments, 73 deaths in the candesartan group and 86 in the amlodipine group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
amlodipine 2.5 to 10 mg QD	mm Hg or DBP ≥90 mm Hg in patients ≥70 years old), with either type 2 diabetes, history of stroke or ischemic attack, left ventricular hypertrophy, proteinuria or serum creatinine ≥1.3 mg/dL		discontinuation due to adverse events	New-onset diabetes occurred in significantly fewer patients in the candesartan group than the amlodipine group (HR, 0.64; 95% CI, 0.43 to 0.97; P=0.033). A total of 125 (5.4%) patients in the candesartan group and 134 (5.8%) of patients in the amlodipine group discontinued due to adverse events.
Taniguchi et al.[173] (2006) Candesartan 8 mg in addition to spironolactone 25 mg QD for 6 months, after 6 months of candesartan monotherapy (combination group) vs candesartan 8 mg daily for 12 months	DB, RCT, XO Patients, 67 years of age on average, with essential HTN and left ventricular hypertrophy	N=97 1 year	Primary: Change in blood pressure and relative wall thickness Secondary: Not reported	Primary: Both study groups experienced a statistically significant reduction in blood pressure from baseline (P<0.05). While candesartan was associated with a significant reduction in relative wall thickness among patients with concentric left ventricular remodeling or hypertrophy (P<0.05), the addition of spironolactone did not provide additional benefit. Secondary: Not reported
Montalescot et al.[174] (2009) ARCHIPELAGO Enalapril 10 mg QD, followed by	AC, DB, MC, RCT Adults with non-ST elevation ACS	N=429 60 days	Primary: Change from baseline in high-sensitivity C-reactive protein at day 60	Primary: High-sensitivity C-reactive protein levels were comparable in both treatment groups (irbesartan: 15.2 mg/L at baseline, 6.5 mg/L at day 60; absolute change of -8.7 mg/L; enalapril: 12.6 mg/L at baseline, 5.5 mg/L at day 60; absolute change of -7.1 mg/L, P value not significant). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
20 mg QD on day 15 vs irbesartan 150 mg QD, followed by 300 mg QD on day 15			Secondary: Changes in other inflammatory markers such as troponin I	Similarly, mean levels of markers of myocardial injury (troponin I) and endothelial dysfunction (microalbuminuria) also decreased from baseline to day 60, with no significant differences between treatment groups.
Solomon et al.[175] (2009) ALLAY Losartan 100 mg QD vs aliskiren 300 mg QD vs aliskiren 300 mg and losartan 100 mg QD	AC, RCT Adults with HTN and increased left ventricular wall thickness	N=465 9 months	Primary: Change in left ventricular mass Secondary: Not reported	Primary: There were reductions in left ventricular mass from baseline in all treatment groups, with 4.9-g/m^2 (5.4%), 4.8-g/m^2 (4.7%), and 5.8-g/m^2 (6.4%) reductions in the aliskiren, losartan, and combination arms, respectively (P<0.0001 for all treatment groups). The reduction in left ventricular mass in the combination group was not significantly different from that with losartan alone (P=0.52). The difference in left ventricular mass regression between the aliskiren and losartan arms was within the prespecified non-inferiority margin, suggesting that aliskiren was as effective as losartan in reducing left ventricular hypertrophy (P<0.0001 for non-inferiority). Secondary: Not reported
Fliser et al.[176] (2004) EUTOPIA Olmesartan 20 mg/day vs placebo	DB, PC, PG, RCT Patients ≥18 years old with HTN, atherosclerotic disease, type 2 diabetes mellitus, and/or LDL-C between 3.89 to 6.48 mmol/L	N=199 12 weeks	Primary: Evaluate anti-inflammatory effects of olmesartan using a panel of inflammation markers: high-sensitivity C-reactive protein, high-sensitivity	Primary: After six weeks of therapy, olmesartan treatment significantly reduced serum levels of C-reactive protein (-15.1%; P<0.05), tumor necrosis factor-α (-8.9%; P<0.02), interleukin-6 (-14.0%; P<0.05) and monocyte chemotactic protein-1 (-6.5%; P<0.01), whereas placebo treatment had no major effect on inflammation markers. After 12 weeks of therapy, C-reactive protein (-21.1%; P<0.02), tumor necrosis factor-α (-13.6%; P<0.01), and interleukin-6 (-8.0%; P<0.01) decreased further with olmesartan and pravastatin cotherapy, but treatment with pravastatin alone did not significantly alter inflammation markers.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
All patients received pravastatin 20 mg/day after six weeks of therapy.			tumor necrosis factor-α, interleukin-6 Secondary: Not reported	In contrast, addition of pravastatin led to a significant (P<0.001) reduction in LDL-C in the olmesartan and placebo groups (-15.1 and -12.1%, respectively). Secondary: Not reported
Rosendorff et al.[177] (2009) Olmesartan 20 to 40 mg QD vs amlodipine 5 to 10 mg QD	DB, AC, RCT Adults with HTN and left ventricular hypertrophy	N=102 52 weeks	Primary: Change in left ventricular mass from baseline to 52 weeks Secondary: Change in left ventricular mass after 26 weeks of treatment	Primary: Mean±SD left ventricular masses of 252.9±73.06 g in the olmesartan group and 236.9±59.94 g in the amlodipine group at baseline were decreased to 248.2±69.31 and 223.9±53.18 g, respectively, after 52 weeks of therapy. Neither of these changes was significantly different from baseline, and the difference between the two treatment groups was not significant. Secondary: At 26 weeks, adjusted percent changes in left ventricular mass were 8.0% with olmesartan and 6.0% with amlodipine. Changes occurring at the 26-week assessment were not significantly different from baseline or from each other.
ONTARGET Investigators[178] (2008) Ramipril 10 mg/day vs telmisartan 80 mg/day vs ramipril 10 mg/day and telmisartan 80 mg/day	DB, MC, PC, RCT Patients with coronary, peripheral, or cerebrovascular disease or diabetes with end-organ damage	N=25,620 56 months (median follow-up)	Primary: Death from cardiovascular causes, MI, stroke or hospitalization for heart failure Secondary: Composite of death from cardiovascular causes, MI or stroke; heart failure, worsening or new angina, new diagnosis diabetes mellitus, new atrial fibrillation, renal impairment, revascularization procedures	Primary: The primary outcome occurred in 16.5, 16.7, and 16.3% of patients receiving ramipril, telmisartan and combination therapy, respectively. Secondary: The composite of death from cardiovascular causes, MI or stroke occurred in 14.1% of patients in the ramipril group and 13.9% of patients in the telmisartan group (RR, 0.99; 95% CI, 0.91 to 17; P=0.001 for non-inferiority). Combination therapy was not significantly better than ramipril alone (RR, 0.99; 95% CI, 0.92 to 17). There were no significant differences in the rates of secondary outcomes, except for renal dysfunction, which occurred in 10.2% of patients receiving ramipril, 10.6% of patients receiving telmisartan and 13.5% of patients receiving combination therapy (P<0.001 vs ramipril; P value not reported vs telmisartan). As compared to the ramipril group, the telmisartan group had lower rates of cough (1.1 vs 4.2%; P<0.001) and angioedema (0.1 vs 0.3%; P=0.01) and a higher rate of hypotensive symptoms (2.6 vs 1.7%; P<0.001); the rate of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				syncope was the same in the two groups (0.2%). As compared to the ramipril group, combination therapy had an increased risk of hypotensive symptoms (4.8 vs 1.7%; P<0.001), syncope (0.3 vs 0.2%; P=0.03) and renal dysfunction (13.5 vs 10.2%; P<0.001).
Mann et al.[179] (2013) ONTARGET Ramipril with telmisartan	Subanalysis Patients in the ONTARGET trial with diabetes mellitus	N=3163 with CKD N=6465 no CKD 56 months	Primary: Composite of death from cardiovascular cause, nonfatal MI, nonfatal stroke or hospitalization for CHF Secondary: composite renal outcome for this analysis was defined posthoc as chronic dialysis (>2 months) or a doubling of baseline serum creatinine	Primary: The stroke rate in all participants with diabetes was not different between the treatment groups, 1.19 and 1.22 per 100 patient-years in those on dual and monotherapy, respectively (HR, 0.99; 95% CI, 0.82 to 1.20). The results were consistent in those with or without renal disease (P value for interaction =0.60; 1.59 vs 1.55 and 1.01 vs 1.08 strokes per 100 patient-years, respectively). Results for other major outcomes indicated no differences and no interaction of renal subgroups with treatment effects. Secondary: Dialysis-dependent acute kidney injury tended to occur more frequently in those allocated to dual than with monotherapy, 0.14 vs 0.08 cases per 100 patient-years, (HR, 1.55; 95% CI, 0.84 to 2.85), and hyperkalemia was more frequent, 1.82 vs 1.07 cases per 100 patient-years (HR, 1.71; 95% CI, 1.44 to 2.02). Both adverse outcomes were more frequent in those with renal disease; however, the excess due to dual therapy was similar in those with and without renal disease.
Julius et al.[180] (2004) VALUE Valsartan 80 to 160 mg QD vs amlodipine 5 to 10 mg QD	DB, PG, RCT Patients ≥50 years old with treated or untreated HTN and history of cardiovascular disease, stroke, or diabetes, previous medications were discontinued at trial onset	N=15,245 4.2 years (mean)	Primary: Time to first cardiac event (cardiac morbidity and mortality) Secondary: Fatal and nonfatal MI, fatal and nonfatal heart failure and fatal and nonfatal stroke, all-cause mortality, new onset diabetes	Primary: There were no differences in the primary composite end point between the valsartan and amlodipine groups (10.6 vs 10.4%; P=0.49). Secondary: There was a higher incidence of myocardial infarction (4.8 vs 4.1%; P=0.02) in patients receiving valsartan than amlodipine. There was no difference in the incidence of heart failure (4.6 vs 5.3%; P=0.12), stroke (4.2 vs 3.7%; P=0.08), and all-cause mortality (11 vs 10.8%; P=0.45) between valsartan- and amlodipine-treated patients. New onset diabetes occurred less with valsartan (13.1%) vs amlodipine (16.4%; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Combined target blood pressure (<140/90 mm Hg) was achieved in 58% and 62% of patients receiving valsartan and amlodipine, respectively.
Zanchetti et al.[181] (2006) VALUE Amlodipine 5 mg QD vs valsartan 80 mg QD	Subgroup analysis of VALUE Patients with HTN	N=15,245 4.2 years	Primary: Time to first cardiac event, analyzed by subgroup Secondary: MI, heart failure and stroke	Primary: The only significant result of the analyses by subgroup for time to first cardiac event was sex; women in the valsartan group experienced more cardiac events as compared to men in the valsartan group (HR for women, 1.21; 95% CI, 13 to 1.42; HR for men, 0.94; 95% CI, 0.82 to 17; P=0.016). The VALUE trial showed no difference in the primary outcome as well as in cardiac morbidity and mortality between amlodipine treatment and valsartan treatment. SBP and DBP were lower, as was incidence of MI, in the amlodipine treatment group as compared to the valsartan group. Secondary: Male patients treated with valsartan had a significantly lower incidence of heart failure than males treated with amlodipine (P<0.001 for male vs female difference; for men, HF rates with valsartan were 4.1% vs amlodipine 5.8% [HR, 0.73; 95% CI, 0.60 to 0.88]; for women, rates were valsartan 5.3% vs amlodipine 4.6%, [HR, 1.18; 95% CI, 0.95 to 1.47]). Patients without a history of stroke had a greater reduction in stroke risk if treated with amlodipine (valsartan 3.4% vs amlodipine 2.6%; HR, 1.34; 95% CI, 19 to 1.65).
Sawada et al.[182] (2009) KYOTO HEART Valsartan up to 160 mg QD plus an additional antihypertensive agent (other than an ACE inhibitor) if necessary to reach target blood pressure <140/90	MC, OL, BE, RCT Japanese adults with uncontrolled HTN and coronary artery disease, cerebral vascular disease, or peripheral vascular disease.	N=3,031 Median 3.27 years	Primary: New onset cardiovascular or cerebrovascular events (stroke, TIA, acute MI, unstable angina, aortic aneurysm, emergency thrombosis, lower limb arterial obstruction, transition to	Primary: In both groups, blood pressure was identical at baseline and at the end of study (157/88 and 133/76, respectively). The primary endpoint was recorded in fewer patients given valsartan add-on (5.5%) than in those given additional non-ARB treatment (10.2%; HR, 0.55; 95% CI, 0.42-0.72; P=0.00001). The difference in the number of primary endpoints was mainly attributable to reduced frequency of stroke and TIA, and unstable angina. These benefits cannot be explained by a difference in blood pressure control. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
or <130/80 mm Hg vs antihypertensive agents (other than ACE inhibitors and ARBs) to reach target blood pressure <140/90 or <130/80 mm Hg			dialysis) Secondary: Not reported	Not reported
The GISSI-AF Investigators[183] (2009) GISSI-AF Valsartan up to 320 mg QD vs placebo	MC, DB, PC, RCT Adults in sinus rhythm who had a recent history of documented atrial fibrillation	N=1,442 1 year	Primary: Time to a first occurrence of atrial fibrillation and proportion of patients who had more than one recurrence of atrial fibrillation over the course of 1 year Secondary: Not reported	Primary: Atrial fibrillation recurred in 371 of the 722 patients (51.4%) in the valsartan group, as compared to 375 of 720 (52.1%) in the placebo group (adjusted HR, 0.97; 96% CI, 0.83 to 1.14; P=0.73). More than one episode of atrial fibrillation occurred in 194 of 722 patients (26.9%) in the valsartan group and in 201 of 720 (27.9%) in the placebo group (adjusted OR, 0.89; 99% CI, 0.64 to 1.23; P=0.34). Secondary: Not reported
The Navigator Study Group[184] (2010) NAVIGATOR Valsartan up to 160 mg QD or matching placebo and nateglinide or matching placebo	DB, MC, RCT Adults with impaired glucose tolerance and established cardiovascular disease or cardiovascular risk factors.	N=9,306 5 years	Primary: Incidence of diabetes and a composite of death from cardiovascular causes, nonfatal MI, nonfatal stroke, hospitalization for heart failure, arterial revascularization, or hospitalization for unstable angina	Primary: The cumulative incidence of diabetes was 33.1% in the valsartan group, as compared to 36.8% in the placebo group (HR in the valsartan group, 0.86; 95% Cl, 0.80 to 0.92; P<0.001). Valsartan, as compared to placebo, did not significantly reduce the incidence of the composite cardiovascular outcome (14.5% vs 14.8%; HR, 0.96; 95% Cl, 0.86 to 17; P=0.43). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Not reported	
Blood Pressure Lowering Treatment Trialists' Collaboration[185] (2007) ACE inhibitors (17 trials) vs ARBs (9 trials)	MA Patients with high blood pressure, diabetes, history or CHD or cerebrovascular disease	N=146,838 (26 trials) Variable duration	Primary: Nonfatal MI or death from CHD, including sudden death; heart failure causing death or requiring hospitalization; nonfatal stroke or death from cerebrovascular disease Secondary: Not reported	Primary: From a total of 146,838 individuals with high blood pressure or an elevated risk of cardiovascular disease, major cardiovascular events were documented in 22,666 patients during follow-up. The analyses showed comparable blood pressure-dependent reductions in risk with ACE inhibitors and ARBs (P≥0.3 for all three outcomes). ACE inhibitors produced a blood pressure-independent reduction in the relative risk of CHD of approximately 9% (95% CI, 3 to 14%). No similar effect was detected for ARBs, and there was some evidence of a difference between ACE inhibitors and ARBs in this regard (P=0.002). For both stroke and heart failure, there was no evidence of any blood pressure-independent effects of either ACE inhibitors or ARBs. Secondary: Not reported

*Agent not available in the United States.
Study regimen abbreviations: QD=once daily, SR=sustained-release, TID=three times daily
Study design abbreviations: AC=active comparator, DB=double blind, DD=double dummy, ES=extension study, MA=meta-analysis, MC=multicenter, OL=open-label, OS=observational, PC=placebo controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, XO=cross-over
Miscellaneous abbreviations: ABPM=ambulatory blood pressure monitoring, ACE inhibitor=angiotensin converting enzyme inhibitor, ARB=angiotensin II receptor blocker, ACS=acute coronary syndrome, BMI=body mass index, CHD=coronary heart disease, CHF=congestive heart failure, CI=confidence interval, DBP=diastolic blood pressure, ESRD=end stage renal disease, eGFR=estimated glomerular filtration rate, GFR=glomerular filtration rate, HbA_{1c}=glycosylated hemoglobin, HCTZ=hydrochlorothiazide, HDL-C=high-density lipoprotein cholesterol, HR=hazard ratio, HTN=hypertension, LDL-C=low-density lipoprotein cholesterol, LSM=least squares mean, LVEF=left ventricular ejection fraction, MAP=mean arterial pressure, MI=myocardial infarction, MMSE=Mini Mental State Examination, NYHA=New York Heart Association, OR=odds ratio, RR=relative risk, QOL=quality of life, Sc=serum creatinine, SD=standard deviation, SBP=systolic blood pressure, TC=total cholesterol, TG=triglycerides, TIA=transient ischemic attack, UAER=urinary albumin excretion rate, WHO=World Health Organization, WMD=weighted mean difference

Additional Evidence

Dose Simplification
Sung et al. evaluated adherence rates with a triple component single pill regimen of olmesartan 20 mg/amlodipine 5 mg/hydrochlorothiazide 12.5 mg compared to the equivalent two-pill regimen of olmesartan 20 mg/hydrochlorothiazide 12.5 mg plus amlodipine 5 mg for 12 weeks. The single-pill group had significantly higher percentage of doses taken than the two-pill group with median (25 to 75 percentile) of 95.1 (95% confidence interval [CI], 86.7 to 100.0) versus 92.1 (95% CI, 73.0 to 97.3) as well as a significantly higher prescribed dose taken correctly with median (25 to 75 percentile) of 91.0 (95% CI, 79.4 to 96.5) versus 88.6 (95% CI, 69.2 to 96.3), P = 0.04 for both comparisons.[186]

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 12. Relative Cost of the Angiotensin II Receptor Antagonists

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Azilsartan	tablet	Edarbi®	$$$$$	N/A
Candesartan	tablet	Atacand®*	$$$$$	$
Irbesartan	tablet	Avapro®*	$$$$$	$
Losartan	tablet	Cozaar®*	$$$$	$
Olmesartan	tablet	Benicar®*	$$$$$	$
Telmisartan	tablet	Micardis®*	$$$$	$
Valsartan	tablet	Diovan®*	$$$$$	$
Combination Products				
Azilsartan and chlorthalidone	Tablet	Edarbyclor®	$$$$	N/A
Candesartan and HCTZ	tablet	Atacand HCT®*	$$$$$	$$
Irbesartan and HCTZ	tablet	Avalide®*	$$$$$	$

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Losartan and HCTZ	tablet	Hyzaar®*	$$$$$	$
Olmesartan and amlodipine and hydrochlorothiazide	tablet	Tribenzor®*	$$$$$	$$$
Olmesartan and HCTZ	tablet	Benicar HCT®*	$$$$$	$
Telmisartan and amlodipine	tablet	Twynsta®*	$$$$$	$$$
Telmisartan and HCTZ	tablet	Micardis HCT®*	$$$$	$$
Valsartan and HCTZ	tablet	Diovan HCT®*	$$$$$	$

*Generic is available in at least one dosage form or strength.
HCTZ=hydrochlorothiazide, N/A=not available

X. Conclusions

All of the angiotensin II receptor blockers (ARBs) are approved for the treatment of hypertension. Some of the products are also approved for the treatment of diabetic nephropathy (irbesartan and losartan), heart failure (candesartan and valsartan), post-myocardial infarction (valsartan), as well as cardiovascular and cerebrovascular risk reduction (telmisartan and losartan, respectively).[3-19] The ARBs are available as single entity products, and most are also available in combination with hydrochlorothiazide. Azilsartan is available in combination with chlorthalidone, telmisartan is available in combination with amlodipine, and olmesartan is available in combination with amlodipine and hydrochlorothiazide (triple therapy). There are other ARBs that are available in combination with amlodipine (olmesartan and valsartan); however, these products are included in the dihydropyridines class review (AHFS Class 242808). All single entity products with the exception of azilsartan are available generically. Fixed-dose combination products are available in a generic formulation with the exception of azilsartan-chlorthalidone.

National and international guidelines recommend the use of ACE inhibitors or ARBs in patients with cerebrovascular disease, coronary artery disease, heart failure, hypertension, left ventricular dysfunction, left ventricular hypertrophy, diabetes, diabetic nephropathy, previous myocardial infarction, and renal disease.[21-39] In general, guidelines do not give preference to one ARB over another.[21-39] Some of the guidelines specifically recommend the use of ACE inhibitors as initial therapy, with the subsequent use of ARBs in patients who do not tolerate ACE inhibitors.[21,23-30,35] Thiazide-type diuretics are frequently recommended as initial therapy in patients with uncomplicated hypertension.[31-36] According to the National Heart, Lung, and Blood Institute's Eighth Report of The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8), thiazide-type diuretics should be utilized first-line for most patients with hypertension, either alone or in combination with another hypertensive from a different medication class (e.g., ACE inhibitors, ARBs, β-blockers, calcium channel blockers).[31] Several guidelines consistently recommend that the selection of an antihypertensive agent be based on compelling indications for use.[31-38] Most patients will require more than one antihypertensive medication to achieve blood pressure goals.[31-35]

Numerous clinical trials have shown that the ARBs can effectively lower systolic and diastolic blood pressure, administered alone or in combination with other antihypertensive agents. Some comparative trials have demonstrated slight differences in blood pressure effects among the various ARBs; however, the clinical significance of these differences remains to be established.[74-170] Guidelines do not give preference to one ARB over another for the treatment of hypertension. Most patients will require more than one antihypertensive agent to achieve blood pressure goals.[31-35] The use of a fixed-dose combination product may simplify the treatment regimen and improve adherence.[33-34,37,186] However, there are no prospective, randomized trials that have demonstrated better clinical outcomes with a fixed-dose combination product compared to the coadministration of the individual components as separate formulations.

ARBs have been shown to reduce cardiovascular morbidity and mortality, as well as preserve renal function.[40-63] The use of losartan also decreases the risk of stroke in patients with hypertension and left ventricular hypertrophy.[6,13] It should be noted that the ACE inhibitors have also been shown to positively impact these endpoints as well (please refer to ACE inhibitor class review for additional information). Several studies comparing ARBs and ACE inhibitors have demonstrated similar efficacy with regards to cardiovascular events, heart failure and the rate of progression of nephropathy.[40,41,43,45,50-54,57,63,65,70-73,178] ACE inhibitors inhibit the

breakdown of bradykinin, which may lead to the development of a persistent non-productive cough. The ARBs do not increase bradykinin and may be better tolerated in some patients.[19,20]

The FDA has evaluated data from two clinical trials (ROADMAP and ORIENT) in which patients with type 2 diabetes who were taking olmesartan had a higher rate of death from cardiovascular causes compared to those who were taking placebo. After the review was completed in April 2011, the FDA has determined that the benefits of olmesartan continue to outweigh its potential risks when used for the treatment of patients with high blood pressure according to the approved drug label. Of note, olmesartan is not recommended as a treatment to delay or prevent protein in the urine in diabetic patients.[187] In June of 2011, the FDA also concluded that a review of a meta-analysis of 31 randomized-controlled trials comparing ARBs to other treatments found no evidence of an increased risk of incident (new) cancer, cancer-related death, breast cancer, lung cancer, or prostate cancer in patients receiving ARBs.[188]

At this time, there is insufficient evidence to conclude that the angiotensin II receptor antagonists offer a significant clinical advantage over other alternatives in general use. Therefore, all brand angiotensin II receptor antagonists within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand angiotensin II receptor antagonist is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Mineralocorticoid (Aldosterone) Receptor Antagonists
AHFS Class 243220
May 8, 2024

I. Overview

Aldosterone is a component of the renin-angiotensin-aldosterone (RAAS) system, which is responsible for the regulation of extracellular volume and blood pressure. Upon binding to the mineralocorticoid receptor on the distal renal tubule, aldosterone activates the sodium-potassium exchange pump, leading to sodium and water retention, as well as potassium excretion. Increased levels of aldosterone are present in both primary and secondary hyperaldosteronism. Heart failure, hepatic cirrhosis, and the nephrotic syndrome are edematous conditions, which can lead to secondary aldosteronism. Volume depletion and sodium loss due to diuretic therapy may also cause secondary aldosteronism.[1,2]

The mineralocorticoid (aldosterone) receptor antagonists, eplerenone and spironolactone, are approved for the treatment of edema, heart failure, hypertension, hypokalemia, and primary hyperaldosteronism. Eplerenone and spironolactone bind to mineralocorticoid receptors, which blocks the binding of aldosterone.[1-6] They are available as single entity agents, and spironolactone is also available in combination with hydrochlorothiazide. Hydrochlorothiazide inhibits the reabsorption of sodium and chloride in the cortical thick ascending limb of the loop of Henle and the early distal tubules. This action leads to an increase in the urinary excretion of sodium and chloride.[1,2] Finerenone is a novel, non-steroidal, selective mineralocorticoid receptor antagonist that has shown to reduce albuminuria in type 2 diabetes (T2D) patients with chronic kidney disease (CKD), while revealing only a low risk of hyperkalemia. In contrast to steroidal mineralocorticoid receptor antagonists such as spironolactone, finerenone is more selective for the mineralocorticoid receptor.[7-9]

The mineralocorticoid (aldosterone) receptor antagonists that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All of the agents except finerenone are available in a generic formulation. This class was last reviewed in May 2022.

Table 1. Mineralocorticoid (Aldosterone) Receptor Antagonists Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Eplerenone	tablet	Inspra®*	eplerenone
Finerenone	tablet	Kerendia®	none
Spironolactone	suspension, tablet	Aldactone®*, Carospir®	spironolactone
Combination Products			
Spironolactone and hydrochlorothiazide	tablet	Aldactazide®*	spironolactone and hydrochlorothiazide

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the mineralocorticoid (aldosterone) receptor antagonists are summarized in Table 2.

Table 2. Treatment Guidelines Using the Mineralocorticoid (Aldosterone) Receptor Antagonists

Clinical Guideline	Recommendations
American Heart Association/American College of Cardiology/American College of Clinical	• In patients with chronic coronary disease (CCD), high-intensity statin therapy is recommended with the aim of achieving a ≥50% reduction in LDL-C levels to reduce the risk of major adverse cardiovascular events (MACE). • In patients in whom high-intensity statin therapy is contraindicated or not tolerated, moderate-intensity statin therapy is recommended with the aim of

Clinical Guideline	Recommendations
Pharmacy/American Society for Preventive Cardiology/National Lipid Association/ Preventive Cardiovascular Nurses Association **Guideline for the Management of Patients With Chronic Coronary Disease (2023)**[10]	achieving a 30% to 49% reduction in LDL-C levels to reduce the risk of MACE. • In patients with CCD who are judged to be at very high risk and on maximally tolerated statin therapy with an LDL-C level ≥70 mg/dL, ezetimibe can be beneficial to further reduce the risk of MACE. • In patients with CCD who are judged to be at very high risk and who have an LDL-C level ≥70 mg/dL, or a non–high-density lipoprotein cholesterol (HDL-C) level ≥100 mg/dL, on maximally tolerated statin and ezetimibe, a PCSK9 monoclonal antibody can be beneficial to further reduce the risk of MACE. • In patients with CCD on maximally tolerated statin therapy with an LDL-C level <100 mg/dL and a persistent fasting triglyceride level of 150 to 499 mg/dL after addressing secondary causes, icosapent ethyl may be considered to further reduce the risk of MACE and cardiovascular death. • In patients with CCD who are not at very high risk and on maximally tolerated statin therapy with an LDL-C level ≥70 mg/dL, it may be reasonable to add ezetimibe to further reduce the risk of MACE. • In patients with CCD on maximally tolerated statin therapy who have an LDL-C level ≥70 mg/dL, and in whom ezetimibe and PCSK9 monoclonal antibody are deemed insufficient or not tolerated, it may be reasonable to add bempedoic acid or inclisiran (in place of PCSK9 monoclonal antibody) to further reduce LDL-C levels. • In patients with CCD receiving statin therapy, adding niacin, fenofibrate, or dietary supplements containing omega-3 fatty acids are not beneficial in reducing cardiovascular risk. • In adults with CCD, nonpharmacologic strategies are recommended as first-line therapy to lower BP in those with elevated BP (120-129/<80 mmHg). • In adults with CCD who have hypertension, a BP target of <130/<80 mmHg is recommended to reduce CVD events and all-cause death. • In adults with CCD and hypertension (systolic BP ≥130 and/or diastolic BP ≥80 mm Hg), in addition to nonpharmacological strategies, GDMT angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), or beta blockers are recommended as first-line therapy for compelling indications (e.g., recent MI or angina), with additional antihypertensive medications (e.g., dihydropyridine calcium channel blockers [CCB], long-acting thiazide diuretics, and/or mineralocorticoid receptor antagonists) added as needed to optimize BP control. • In patients with CCD and no indication for oral anticoagulant therapy, low-dose aspirin 81 mg (75 to 100 mg) is recommended to reduce atherosclerotic events. • In patients with CCD treated with PCI, dual antiplatelet therapy (DAPT) consisting of aspirin and clopidogrel for 6 months post PCI followed by single antiplatelet therapy (SAPT) is indicated to reduce MACE and bleeding events.* • In select patients with CCD treated with PCI and a drug-eluting stent (DES) who have completed a 1- to 3-month course of DAPT, P2Y12 inhibitor monotherapy for at least 12 months is reasonable to reduce bleeding risk. • In patients with CCD who have had a previous MI and are at low bleeding risk, extended DAPT beyond 12 months for a period of up to 3 years may be reasonable to reduce MACE. • In patients with CCD and a previous history of MI without a history of stroke, transient ischemic attack (TIA), or ICH, vorapaxar may be added to aspirin therapy to reduce MACE. • In patients with CCD, the use of DAPT after CABG may be useful to reduce the incidence of saphenous vein graft occlusion. • In patients with CCD without recent ACS or a PCI-related indication for DAPT, the addition of clopidogrel to aspirin therapy is not useful to reduce MACE. • In patients with CCD and previous stroke, TIA, or ICH, vorapaxar should not be added to DAPT because of increased risk of major bleeding and ICH.

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	• In patients with CCD and previous stroke, TIA, or ICH, prasugrel should not be used because of risk of significant or fatal bleeding. • In patients with CCD, chronic nonsteroidal anti-inflammatory drugs should not be used because of increased cardiovascular and bleeding complications. • In patients with CCD who have undergone elective PCI and who require oral anticoagulant therapy, DAPT for one to four weeks followed by clopidogrel alone for six months should be administered in addition to DOAC. • In patients with CCD who have undergone PCI and who require oral anticoagulant therapy, continuing aspirin in addition to clopidogrel for up to 1 month is reasonable if the patient has a high thrombotic risk and low bleeding risk. • In patients with CCD who require oral anticoagulation and have a low atherothrombotic risk, discontinuation of aspirin therapy with continuation of DOAC alone may be considered one year after PCI to reduce bleeding risk. • In patients with CCD who require oral anticoagulation, DOAC monotherapy may be considered if there is no acute indication for concomitant antiplatelet therapy. • In patients with CCD without an indication for therapeutic DOAC or DAPT and who are at high risk of recurrent ischemic events but low-to-moderate bleeding risk, the addition of low-dose rivaroxaban 2.5 mg twice daily to aspirin 81 mg daily is reasonable for long-term reduction of risk for MACE. • In patients with CCD on DAPT, the use of a PPI can be effective in reducing gastrointestinal bleeding risk. • In patients with CCD and LVEF ≤40% with or without previous MI, the use of beta-blocker therapy is recommended to reduce the risk of future MACE, including cardiovascular death. • In patients with CCD and LVEF<50%, the use of sustained release metoprolol succinate, carvedilol, or bisoprolol with titration to target doses is recommended in preference to other beta blockers. • In patients with CCD who were initiated on beta-blocker therapy for previous MI without a history of or current LVEF ≤50%, angina, arrhythmias, or uncontrolled hypertension, it may be reasonable to reassess the indication for long-term (>1 year) use of beta-blocker therapy for reducing MACE. • In patients with CCD without previous MI or LVEF ≤50%, the use of beta-blocker therapy is not beneficial in reducing MACE, in the absence of another primary indication for beta-blocker therapy. • In patients with CCD who also have hypertension, diabetes, LVEF ≤40%, or CKD, the use of ACE inhibitors, or ARBs if ACE inhibitor–intolerant, is recommended to reduce cardiovascular events. • In patients with CCD without hypertension, diabetes, or CKD and LVEF >40%, the use of ACE inhibitors or ARBs may be considered to reduce cardiovascular events. • In patients with CCD, the addition of colchicine for secondary prevention may be considered to reduce recurrent ASCVD events. • In patients with CCD, an annual influenza vaccination is recommended to reduce cardiovascular morbidity, cardiovascular death, and all-cause death. • In patients with CCD, coronavirus disease 2019 (COVID-19) vaccination is recommended per public health guidelines to reduce COVID-19 complications. • In patients with CCD, a pneumococcal vaccine is reasonable to reduce cardiovascular morbidity and mortality and all-cause death. • In patients with CCD and angina, antianginal therapy with either a beta blocker, CCB, or long-acting nitrate is recommended for relief of angina or equivalent symptoms. • In patients with CCD and angina who remain symptomatic after initial treatment, addition of a second antianginal agent from a different therapeutic class (beta blockers, CCB, long-acting nitrates) is recommended for relief of angina or

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	equivalent symptoms. • In patients with CCD, ranolazine is recommended in patients who remain symptomatic despite treatment with beta blockers, CCB, or long-acting nitrate therapies. • In patients with CCD, sublingual nitroglycerin or nitroglycerin spray is recommended for immediate short-term relief of angina or equivalent symptoms. • In patients with CCD and normal LV function, the addition of ivabradine to standard anti-anginal therapy is potentially harmful. • In patients with CCD and lifestyle-limiting angina despite GDMT and with significant coronary artery stenoses amenable to revascularization, revascularization is recommended to improve symptoms. • In patients with CCD who have experienced SCAD, beta-blocker therapy may be reasonable to reduce the incidence of recurrent SCAD. • Women with CCD who are contemplating pregnancy or who are pregnant should not use ACE inhibitors, ARBs, direct renin inhibitors, angiotensin receptor-neprilysin inhibitors, or aldosterone antagonists during pregnancy to prevent harm to the fetus. • Women with CCD should not receive systemic postmenopausal hormone therapy because of a lack of benefit on MACE and mortality, and an increased risk of venous thromboembolism.
European Society of Cardiology: **Guidelines for the Diagnosis and Management of Chronic Coronary Syndromes (2019)[11]**	<u>Pharmacological management of stable coronary artery disease (CAD) patients</u> • The two aims of the pharmacological management of stable CAD patients are to obtain relief of symptoms and to prevent CV events. • Optimal medical treatment indicates at least one drug for angina/ischaemia relief plus drugs for event prevention. • It is recommended to educate patients about the disease, risk factors and treatment strategy. • It is indicated to review the patient's response soon after starting therapy. • Concomitant use of a proton pump inhibitor is recommended in patients receiving aspirin monotherapy, DAPT, or DOAC monotherapy who are at high risk of gastrointestinal bleeding. • Lipid-lowering drugs: if goals are not met on maximum tolerated dose of a statin, consideration of combination therapy with ezetimibe or a PCSK9 inhibitor is recommended • ACE inhibitors should be considered in patients at a very high risk of cardiovascular adverse events • Angina/ischemia relief: o Short-acting nitrates are recommended. o First-line treatment is indicated with ß-blockers and/or calcium channel blockers to control heart rate and symptoms. o Long-acting nitrates should be considered as a second-line treatment option when initial therapy with a beta-blocker and/or a non-DHP-calcium channel blocker is contraindicated, poorly tolerated, or inadequate in controlling angina symptoms o Nicorandil, ranolazine, ivabradine, or trimetazidine should be considered as a second-line treatment to reduce angina frequency and improve exercise tolerance in subjects who cannot tolerate, have contraindications to, or whose symptoms are not adequately controlled by beta-blockers, CCBs, and long-acting nitrates. o According to comorbidities/tolerance, it is indicated to use second-line therapies as first-line treatment in selected patients. o In asymptomatic patients with large areas of ischaemia (>10%) ß-blockers should be considered. o In patients with vasospastic angina, calcium channel blockers and nitrates should be considered and beta-blockers avoided.

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	• Event prevention:
	  ○ Low-dose aspirin daily is recommended in all stable CAD patients.
	  ○ Clopidogrel is indicated as an alternative in case of aspirin intolerance.
	  ○ Statins are recommended in all stable CAD patients.
	  ○ It is recommended to use ACE inhibitors (or ARBs) if presence of other conditions (e.g., heart failure, hypertension or diabetes).
	
	<u>Treatment in patients with microvascular angina</u>
	• It is recommended that all patients receive secondary prevention medications including aspirin and statins.
	• ß-blockers are recommended as a first-line treatment.
	• Calcium antagonists are recommended if ß-blockers do not achieve sufficient symptomatic benefit or are not tolerated.
	• ACE inhibitors or nicorandil may be considered in patients with refractory symptoms.
	• Xanthine derivatives or nonpharmacological treatments such as neurostimulatory techniques may be considered in patients with symptoms refractory to the above listed drugs.
	
	<u>Stenting and peri-procedural antiplatelet strategies in stable CAD patients</u>
	• Drug-eluting stent (DES) is recommended in stable CAD patients undergoing stenting if there is no contraindication to prolonged dual antiplatelet therapy (DAPT).
	• Aspirin is recommended for elective stenting.
	• Clopidogrel is recommended for elective stenting.
	• Prasugrel or ticagrelor should be considered in patients with stent thrombosis on clopidogrel without treatment interruption.
	• GP IIb/IIIa antagonists should be considered for bailout situation only.
	• Platelet function testing or genetic testing may be considered in specific or high risk situations (e.g., prior history of stent thrombosis; compliance issue; suspicion of resistance; high bleeding risk) if results may change the treatment strategy.
	• Prasugrel or ticagrelor may be considered in specific high risk situations of elective stenting (e.g., left main stenting, high risk of stent thrombosis, diabetes).
	• Pretreatment with clopidogrel (when coronary anatomy is not known) is not recommended.
	• Routine platelet function testing (clopidogrel and aspirin) to adjust antiplatelet therapy before or after elective stenting is not recommended.
	• Prasugrel or ticagrelor is not recommended in low risk elective stenting.
	• After uncomplicated PCI, early cessation (≤1 week) of aspirin, and continuation of dual therapy with oral anticoagulation therapy and clopidogrel should be considered if the risk of stent thrombosis is low
	• Triple therapy with aspirin, clopidogrel, and a DOAC for ≥1 month should be considered when the risk of stent thrombosis outweighs the bleeding risk, with a total of no more than six months
	
	<u>Follow-up of revascularized stable coronary artery disease patients</u>
	• It is recommended that all revascularized patients receive a secondary prevention and be scheduled for follow-up visit.
	• It is recommended to instruct patients before discharge about return to work and reuptake of full activities. Patients have to be advised to seek immediate medical contact if symptoms (re-) occur.
	• Single antiplatelet therapy, usually aspirin, is recommended indefinitely.
	• DAPT is indicated after bare metal stent (BMS) for at least one month.
	• DAPT is indicated for six to 12 months after 2nd generation DES.
	• DAPT may be used for more than one year in patients at high ischemic risk (e.g.,

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	stent thrombosis, recurrent acute coronary syndrome on DAPT, post MI/diffuse CAD) and low bleeding risk. • DAPT for one to three months may be used after DES implantation in patients at high bleeding risk or with undeferrable surgery or concomitant anticoagulant treatment. <u>Antithrombotic therapy in patients with chronic coronary syndrome:</u> • Addition of a second antithrombotic drug to aspirin for long-term secondary prevention should be considered in patients with at least a moderately increased risk of ischemic events and without high bleeding risk • When oral anticoagulation is initiated in patients with AF, a DOAC is recommended in preference to VKA therapy.
American College of Physicians/ American College of Cardiology Foundation/ American Heart Association/ American Association for Thoracic Surgery/ Preventive Cardiovascular Nurses Association/ Society of Thoracic Surgeons: **Management of Stable Ischemic Heart Disease (2012)**[12]	<u>Medical therapy to prevent MI and death in patients with stable IHD</u> • Aspirin 75 to 162 mg daily should be continued indefinitely in the absence of contraindications. • Treatment with clopidogrel is a reasonable option when aspirin in contraindicated. • Dipyridamole should not be used as antiplatelet therapy. • Beta-blocker therapy should be initiated and continued for three years in all patients with normal left ventricular (LV) function following MI or acute coronary syndromes. • Metoprolol succinate, carvedilol, or bisoprolol should be used for all patients with systolic LV dysfunction (ejection fraction ≤40%) with heart failure or prior MI, unless contraindicated. • ACE inhibitors should be prescribed in all patients with stable IHD who also have hypertension, diabetes, LV systolic dysfunction (ejection fraction ≤40%), and/or chronic kidney disease, unless contraindicated. • Angiotensin-receptor blockers (ARBs) are recommended for patients with stable IHD who have hypertension, diabetes, LV systolic dysfunction, or chronic kidney disease and have indications for, but are intolerant of, ACE inhibitors. • Patients should receive an annual influenza vaccine. <u>Medical therapy for relief of symptoms in patients with stable IHD</u> • Beta-blockers are recommended as initial therapy for relief of symptoms. • Calcium channel blockers or long-acting nitrates should be prescribed for relief of symptoms when β-blockers are contraindicated or cause unacceptable side effects. • Calcium channel blockers or long-acting nitrates, in combination with β-blockers, should be prescribed for relief of symptoms when initial treatment with β-blockers is unsuccessful. • Nitroglycerin or nitroglycerin spray should be used for immediate relief of angina. • Ranolazine is a fourth-line agent reserved for patients who have contraindications to, do not respond to, or cannot tolerate β-blockers, calcium-channel blockers, or long-acting nitrates.

American College of Cardiology Foundation/American Heart Association: **2014 American Heart Association/ American College of Cardiology Foundation Guideline for the**	<u>Early hospital care- standard medical therapies</u>
	• Supplemental oxygen should be administered to patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) with arterial oxygen saturation <90%, respiratory distress, or other high risk features of hypoxemia.
	• Anti-ischemic and analgesic medications
	  ○ Nitrates
	  ▪ Patients with NSTE-ACS with continuing ischemic pain should receive sublingual nitroglycerin (0.3 to 0.4 mg) every 5 minutes for up to three doses, after which an assessment should be made about the need for intravenous nitroglycerin.

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Management of Patients With Non–ST-Elevation Acute Coronary Syndromes (2014)[13]	▪ Intravenous nitroglycerin is indicated for patients with NSTE-ACS for the treatment of persistent ischemia, heart failure, or hypertension. ▪ Nitrates should not be administered to patients who recently received a phosphodiesterase inhibitor, especially within 24 hours of sildenafil or vardenafil, or within 48 hours of tadalafil. o Analgesic therapy ▪ In the absence of contraindications, it may be reasonable to administer morphine sulphate intravenously to patients with NSTE-ACE if there is continued ischemic chest pain despite treatment with maximally tolerated anti-ischemic medications. ▪ Nonsteroidal anti-inflammatory drugs (NSAIDs) (except aspirin) should not be initiated and should be discontinued during hospitalization due to the increased risk of major adverse cardiac event associated with their use o Beta-adrenergic blockers ▪ Oral β-blocker therapy should be initiated within the first 24 hours in patients who do not have any of the following: 1) signs of HF, 2) evidence of low-output state, 3) increased risk for cardiogenic shock, or 4) other contraindications to β-blockade (e.g., PR interval >0.24 second, second- or third-degree heart block without a cardiac pacemaker, active asthma, or reactive airway disease) ▪ In patients with concomitant NSTE-ACS, stabilized heart failure, and reduced systolic function, it is recommended to continue β-blocker therapy with one of the three drugs proven to reduce mortality in patients with heart failure: sustained-release metoprolol succinate, carvedilol, or bisoprolol. ▪ Patients with documented contraindications to β-blockers in the first 24 hours should be re-evaluated to determine subsequent eligibility. o Calcium channel blockers (CCBs) ▪ In patients with NSTE-ACS, continuing or frequently recurring ischemia, and a contraindication to β-blockers, a nondihydropyridine CCB (e.g., verapamil or diltiazem) should be given as initial therapy in the absence of clinically significant LV dysfunction, increased risk for cardiogenic shock, PR interval >0.24 seconds, or second or third degree atrioventricular block without a cardiac pacemaker. ▪ Oral nondihydropyridine calcium antagonists are recommended in patients with NSTE-ACS who have recurrent ischemia in the absence of contraindications, after appropriate use of β-blockers and nitrates. ▪ CCBs are recommended for ischemic symptoms when β-blockers are not successful, are contraindicated, or cause unacceptable side effects. ▪ Long-acting CCBs and nitrates are recommended in patients with coronary artery spasm. ▪ Immediate-release nifedipine should not be administered to patients with NSTE-ACS in the absence of β-blocker therapy. o Other anti-ischemic interventions ▪ Ranolazine is currently indicated for treatment of chronic angina; however, it may also improve outcomes in NSTE-ACS patients due to a reduction in recurrent ischemia. o Cholesterol management ▪ High-intensity statin therapy should be initiated or continued in all patients with NSTE-ACS and no contraindications to its use. Treatment with statins reduces the rate of recurrent MI, coronary heart disease mortality, need for myocardial revascularization, and stroke. ▪ It is reasonable to obtain a fasting lipid profile in patients with NSTE-ACS, preferably within 24 hours of presentation. • Inhibitors of renin-angiotensin-aldosterone system

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	○ ACE inhibitors should be started and continued indefinitely in all patients with LVEF <0.40 and in those with hypertension, diabetes mellitus, or stable CKD, unless contraindicated. ○ ARBs are recommended in patients with heart failure or myocardial infarction with LVEF <0.40 who are ACE inhibitor intolerant. ○ Aldosterone-blockade is recommended in patients post-MI without significant renal dysfunction (creatinine >2.5 mg/dL in men or >2.0 mg/dL in women) or hyperkalemia (K >5.0 mEq/L) who are receiving therapeutic doses of ACE inhibitor and β-blocker and have a LVEF <0.40, diabetes mellitus, or heart failure. • Initial antiplatelet/anticoagulant therapy in patients with definite or likely NSTE-ACS treated with an initial invasive or ischemia-guided strategy ○ Non-enteric coated, chewable aspirin (162 to 325 mg) should be given to all patients with NSTE-ACS without contraindications as soon as possible after presentation, and a maintenance dose of aspirin (81 to 162 mg/day) should be continued indefinitely. ○ In patients who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance, a loading dose of clopidogrel followed by a daily maintenance dose should be administered. ○ A $P2Y_{12}$ receptor inhibitor (clopidogrel or ticagrelor) in addition to aspirin should be administered for up to 12 months to all patients with NSTE-ACS without contraindications who are treated with an early invasive or ischemia-guided strategy. Options include: ▪ Clopidogrel: 300 or 600 mg loading dose, then 75 mg daily. ▪ Ticagrelor: 180 mg loading dose, then 90 mg twice daily. ▪ It is reasonable to use ticagrelor in preference to clopidogrel for $P2Y_{12}$ treatment in patients with NSTE-ACS who undergo an early invasive or ischemia-guided strategy. ▪ In patients with NSTE-ACS treated with an early invasive strategy and dual antiplatelet therapy (DAPT) with intermediate/high-risk features (e.g., positive troponin), a GP IIb/IIIa inhibitor may be considered as part of initial antiplatelet therapy. Preferred options are eptifibatide or tirofiban. <u>Percutaneous coronary intervention (PCI)- Antiplatelet and anticoagulant therapy</u> • Antiplatelet agents ○ Patients already taking daily aspirin before PCI should take 81 to 325 mg non-enteric coated aspirin before PCI ○ Patients not on aspirin therapy should be given non-enteric coated aspirin 325 mg as soon as possible before PCI. ○ After PCI, aspirin should be continued indefinitely. ○ A loading dose of a $P2Y_{12}$ inhibitor should be given before the procedure in patients undergoing PCI with stenting. Options include clopidogrel 600 mg, prasugrel 60 mg, or ticagrelor 180 mg. ○ In patients with NSTE-ACS and high-risk features (e.g., elevated troponin) not adequately pretreated with clopidogrel or ticagrelor, it is useful to administer a GP IIb/IIIa inhibitor (abciximab, double-bolus eptifibatide, or high-dose bolus tirofiban) at the time of PCI. ○ In patients receiving a stent (bare metal or drug eluting) during PCI, $P2Y_{12}$ inhibitor therapy should be given for at least 12 months. Options include clopidogrel 75 mg daily, prasugrel 10 mg daily, or ticagrelor 90 mg twice daily. • Anticoagulant therapy ○ An anticoagulant should be administered to patients with NSTE-ACS undergoing PCI to reduce the risk of intracoronary and catheter thrombus formation.

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	○ Intravenous unfractionated heparin (UFH) is useful in patients with NSTE-ACS undergoing PCI. ○ Bivalirudin is useful as an anticoagulant with or without prior treatment with UFH. ○ An additional dose of 0.3 mg/kg intravenous enoxaparin should be administered at the time of PCI to patients with NSTE-ACS who have received fewer than two therapeutic subcutaneous doses or received the last subcutaneous enoxaparin dose eight to 12 hours before PCI. ○ If PCI is performed while the patient is on fondaparinux, an additional 85 IU/kg of UFH should be given intravenously immediately before PCI because of the risk of catheter thrombosis (60 IU/kg IV if a GP IIb/IIIa inhibitor used with UFH dosing based on the target-activated clotting time). ○ Anticoagulant therapy should be discontinued after PCI unless there is a compelling reason to continue. • Timing of CABG in relation to use of antiplatelet agents ○ Non-enteric coated aspirin (81 to 325 mg daily) should be administered preoperatively to patients undergoing CABG. ○ In patients referred for elective CABG, clopidogrel and ticagrelor should be discontinued for at least five days before surgery and prasugrel for at least seven days before surgery. ○ In patients referred for urgent CABG, clopidogrel and ticagrelor should be discontinued for at least 24 hours to reduce major bleeding. ○ In patients referred for CABG, short-acting intravenous GP IIb/IIIa inhibitors (eptifibatide or tirofiban) should be discontinued for at least 2 to 4 hours before surgery and abciximab for at least 12 hours before to limit blood loss and transfusion. <u>Late hospital care, hospital discharge, and posthospital discharge care</u> • Medications at discharge ○ Medications required in the hospital to control ischemia should be continued after hospital discharge in patients with NSTE-ACS who do not undergo coronary revascularization, patients with incomplete or unsuccessful revascularization, and patients with recurrent symptoms after revascularization. Titration of the doses may be required. ○ All patients who are post–NSTE-ACS should be given sublingual or spray nitroglycerin with verbal and written instructions for its use. ○ Before hospital discharge, patients with NSTE-ACS should be informed about symptoms of worsening myocardial ischemia and MI and should be given verbal and written instructions about how and when to seek emergency care for such symptoms. ○ Before hospital discharge, patients who are post–NSTE-ACS and/or designated responsible caregivers should be provided with easily understood and culturally sensitive verbal and written instructions about medication type, purpose, dose, frequency, side effects, and duration of use. ○ For patients who are post–NSTE-ACS and have initial angina lasting more than one minute, nitroglycerin (one dose sublingual or spray) is recommended if angina does not subside within three to five minutes; call 9-1-1 immediately to access emergency medical services. ○ If the pattern or severity of angina changes, suggesting worsening myocardial ischemia (e.g., pain is more frequent or severe or is precipitated by less effort or occurs at rest), patients should contact their clinician without delay to assess the need for additional treatment or testing. ○ Before discharge, patients should be educated about modification of cardiovascular risk factors. • Late hospital and post-hospital oral antiplatelet therapy ○ Aspirin should be continued indefinitely. The dose should be 81 mg daily in

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	patients treated with ticagrelor and 81 to 325 mg daily in all other patients. o In addition to aspirin, a $P2Y_{12}$ inhibitor (either clopidogrel or ticagrelor) should be continued for up to 12 months in all patients with NSTE-ACS without contraindications who are treated with an ischemia-guided strategy. o In patients receiving a stent (bare-metal stent or DES) during PCI for NSTE-ACS, P2Y12 inhibitor therapy should be given for at least 12 months. • Combined oral anticoagulant therapy and antiplatelet therapy in patients with NSTE-ACS o The duration of triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a $P2Y_{12}$ receptor inhibitor in patients with NSTE-ACS should be minimized to the extent possible to limit the risk of bleeding. o Proton pump inhibitors should be prescribed in patients with NSTE-ACS with a history of gastrointestinal bleeding who require triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a $P2Y_{12}$ receptor inhibitor.
European Society of Cardiology: **Guidelines for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation (2020)[14]**	<u>Pharmacological treatment of ischemia</u> • Sublingual or intravenous nitrates and early initiation of β-blocker treatment is recommended in patients with ongoing ischemic symptoms and without contraindications. • Continuation of chronic β-blocker therapy is recommended unless the patient is in overt heart failure • Sublingual or intravenous nitrates are recommended to relieve angina; intravenous treatment is recommended in patients with recurrent angina, uncontrolled hypertension, or signs of heart failure. • In patients with suspected/confirmed vasospastic angina, calcium channel blockers, and nitrates should be considered and β-blockers avoided. <u>Recommendations for platelet inhibition in non-ST-elevation acute coronary syndromes</u> • Aspirin is recommended for all patients without contraindications at an initial oral loading dose of 150 to 300 mg (in aspirin-naïve patients) and a maintenance dose of 75 to 100 mg/day long-term regardless of treatment strategy. • A $P2Y_{12}$ inhibitor is recommended, in addition to aspirin, for 12 months unless there are contraindications such as excessive risks of bleeds. o Ticagrelor (180 mg loading dose, 90 mg twice daily) is recommended, in the absence of contraindication, for all patients at moderate-to-high risk of ischemic events (e.g., elevated cardiac troponins), regardless of initial treatment strategy and including those pretreated with clopidogrel (which should be discontinued when ticagrelor is started). o Prasugrel (60 mg loading dose, 10 mg daily dose) is recommended in patients who are proceeding to PCI if no contraindication. Prasugrel should be considered in preference to ticagrelor in NSTE-ACS patients who proceed to PCI. o Clopidogrel (300 to 600 mg loading dose, 75 mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel or who require oral anticoagulation. • $P2Y_{12}$ inhibitor administration for a shorter duration of three to six months after DES implantation may be considered in patients deemed at high bleeding risk. • Pre-treatment with a $P2Y_{12}$ inhibitor may be considered in patients with NSTE-ACS who are not planned to undergo an early invasive strategy. • It is not recommended to administer routine pre-treatment with a $P2Y_{12}$ inhibitor in patients in whom coronary anatomy is not known. • It is not recommended to administer prasugrel in patients whom coronary anatomy is not known. • GPIIb/IIIa inhibitors during PCI should be considered for bailout situations or thrombotic complications.

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	• Cangrelor may be considered in $P2Y_{12}$ inhibitor-naïve patients undergoing PCI. • It is not recommended to administer GPIIb/IIIa inhibitors in patients whom coronary anatomy is not known. • $P2Y_{12}$ inhibitor administration in addition to aspirin beyond one year may be considered after careful assessment of the ischemic and bleeding risks of the patient. <u>Recommendations for anticoagulation in non-ST-elevation acute coronary syndromes</u> • Parenteral anticoagulation is recommended at the time of diagnosis according to both ischemic and bleeding risks. • Fondaparinux is recommended as having the most favorable efficacy-safety profile regardless of the management strategy. • Bivalirudin is recommended as an alternative to UFH plus GPIIb/IIIa inhibitors during PCI. • UFH is recommended in patients undergoing PCI who did not receive any anticoagulant. • In patients on fondaparinux undergoing PCI, a single intravenous bolus of UFH is recommended during the procedure. • Enoxaparin or UFH are recommended when fondaparinux is not available. • Enoxaparin should be considered as an anticoagulant for PCI in patients pretreated for PCI with subcutaneous enoxaparin. • Additional activated clotting time-guided intravenous boluses of UFH during PCI may be considered following initial UFH treatment. • Discontinuation of anticoagulation should be considered after PCI, unless otherwise indicated. • Crossover between UFH and LMWH is not recommended. • In NSTEMI patients with no prior stroke/TIA and at high ischemic risk as well as low bleeding risk receiving aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily for approximately one year) may be considered after discontinuation of parenteral anticoagulation. <u>Recommendations for combining antiplatelet agents and anticoagulants in non-ST-elevation acute coronary syndrome patients requiring chronic oral anticoagulation</u> • In patients with a firm indication for oral anticoagulation (e.g., atrial fibrillation with a $CHADS_2$-VASc score ≥2, recent VTE, mechanical valve prosthesis), oral anticoagulation is recommended in addition to antiplatelet therapy. • An early invasive coronary angiography (within 24 hours) should be considered in moderate- to high-risk patients, irrespective of oral anticoagulant exposure, to expedite treatment allocation (medical vs PCI vs CABG) and to determine optimal antithrombotic regimen. • Initial dual antiplatelet therapy with aspirin plus a $P2Y_{12}$ inhibitor in addition to oral anticoagulation before coronary angiography is not recommended. • During PCI, additional parenteral anticoagulation is recommended, irrespective of the timing of the last dose of all non-vitamin K antagonist oral anticoagulants (NOACs) and if INR is <2.5 in VKA-treated patients. • Uninterrupted therapeutic anticoagulation with VKA or NOACs should be considered during the periprocedural phase. • Periprocedural DAPT administration consisting of aspirin and clopidogrel up to one week is recommended • Discontinuation of antiplatelet treatment in patients treated with an oral anticoagulant is recommended after 12 months • Following coronary stenting, dual (oral) antiplatelet therapy (DAPT) including new $P2Y_{12}$ inhibitors should be considered as an alternative to triple therapy for patients with non-ST-elevation acute coronary syndromes and atrial fibrillation with a $CHADS_2$-VASc score of 1 (in males) or 2 (in females).

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	• If at low bleeding risk (HAS-BLED ≤2), triple therapy with oral anticoagulant, aspirin, and clopidogrel should be considered for six months, followed by oral anticoagulant and aspirin or clopidogrel continued up to 12 months. • If at high bleeding risk (HAS-BLED ≥3), triple therapy with oral anticoagulant, aspirin, and clopidogrel should be considered for one month, followed by oral anticoagulant and aspirin or clopidogrel continued up to 12 months irrespective of the stent type. • Dual therapy with oral anticoagulant and clopidogrel may be considered as an alternative to triple antithrombotic therapy in selected patients (HAS-BLED ≥3 and low risk of stent thrombosis). • The use of ticagrelor or prasugrel as part of triple therapy is not recommended. • In medically managed patients, one antiplatelet agent in addition to oral anticoagulant should be considered for up to one year. <u>Recommendations for post-interventional and maintenance treatment</u> • In patients with NSTE-ACS with coronary stent implantation, DAPT with a $P2Y_{12}$ inhibitor on top of aspirin is recommended for 12 months unless there are contraindications such as excessive risk of bleeding. • Adding a second anti-thrombotic agent to aspirin for extended long-term secondary prevention should be considered in patients with a moderate to high risk of ischemic events and without increased risk of major bleeding. • After stent implantation with high risk of bleeding, discontinuation of $P2Y_{12}$ inhibitor therapy after three months should be considered • After stent implantation in patients undergoing DAPT, stopping aspirin after three to six months should be considered, depending on balance between ischemic and bleeding risk. • De-escalation of $P2Y_{12}$ inhibitor treatment may be considered as an alternative DAPT strategy, especially for ACS patients deemed unsuitable for potent platelet inhibition.
American College of Cardiology/American Heart Association: **Guideline for the Management of ST-Elevation Myocardial Infarction (2013)**[15]	<u>Routine medical therapies: β-blockers</u> • Oral β-blockers should be initiated within the first 24 hours in patients with an ST-segment elevation myocardial infarction (STEMI) who do not have any of the following: 1) signs of heart failure, 2) evidence of a low-output state, 3) increased risk of cardiogenic shock, 4) other contraindications to use of oral β-blockers (e.g., PR interval >24 seconds, second or third degree heart block, active asthma, reactive airway disease). • β-blockers should be continued during and after hospitalization for all patients with STEMI and with no contraindications to their use. • Patients with initial contraindications to the use of β-blockers in the first 24 hours after STEMI should be re-evaluated to determine their subsequent eligibility. • It is reasonable to administer intravenous β-blockers at the time of presentation to patients with STEMI and no contraindications to their use who are hypertensive or have ongoing ischemia. <u>Routine medical therapies: renin-angiotensin-aldosterone system inhibitors</u> • An ACE inhibitor should be administered within the first 24 hours to all patients with ST-segment elevation myocardial infarction with anterior location, heart failure, or ejection fraction ≤40%, unless contraindicated. • An ARB should be given to patients who have indications for but are intolerant of ACE inhibitors. • ACE inhibitors are reasonable for all patients with no contraindications to their use. • An aldosterone antagonist should be given to patients with STEMI and no contraindications who are already receiving an ACE inhibitor and β-blocker and who have an EF ≤40% and either symptomatic heart failure or diabetes.

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	Routine medical therapies: Lipid management • High-intensity statin therapy should be initiated or continued in all patients with STEMI and no contraindications to its use. • It is reasonable to obtain a fasting lipid profile in patients with STEMI, preferably within 24 hours of presentation.
European Society of Cardiology: **Management of Acute Myocardial Infarction in Patients Presenting with ST-segment Elevation (2017)[16]**	Routine therapies in the acute, subacute and long term phase of ST-elevation myocardial infarction (STEMI) • Antiplatelet therapy with low dose aspirin (75 to 100 mg) is indicated indefinitely after STEMI. • Dual antiplatelet therapy with a combination of aspirin and prasugrel or aspirin and ticagrelor is recommended for 12 months after percutaneous coronary intervention (PCI), unless there are contraindications such as excessive risk of bleeding. • A proton pump inhibitor (PPI) in combination with dual antiplatelet therapy is recommended in patients at high risk of gastrointestinal bleeding. • In patients with an indication for oral anticoagulation, oral anticoagulants are indicated in addition to antiplatelet therapy. • In patients who are at high risk of severe bleeding complications, discontinuation of $P2Y_{12}$ inhibitor therapy after six months should be considered. • In STEMI patients with stent implantation and an indication for oral anticoagulation, triple therapy (oral anticoagulant, aspirin, and clopidogrel) should be considered for one to six months (according a balance between the estimated risk of recurrent coronary events and bleeding). • In patients with left ventricular thrombus, anticoagulation should be instituted for a minimum of six months, guided by repeated imaging. • In selected patients who receive aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily) may be considered if the patient is at low bleeding risk. • Dual antiplatelet therapy should be used up to one year in patients with STEMI who did not receive a stent unless there are contraindications such as excessive risk of bleeding. • In high ischemic-risk patients (age ≥50 years, and at least one of the following risk factors: age ≥65 years, diabetes mellitus on medication, prior spontaneous MAI, multivessel CAD, or chronic renal dysfunction with eGFR <60 mL/min) who have tolerated dual antiplatelet therapy without a bleeding complication, treatment with dual antiplatelet therapy in the form of ticagrelor 60 mg twice a day on top of aspirin for longer than 12 months may be considered for up to three years. • The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with aspirin and oral anticoagulation. • Oral treatment with β-blockers should be considered during hospital stay and continued thereafter in all patients without contraindications. • Oral treatment with β-blockers is indicated in patients with heart failure or left ventricular dysfunction, LVEF ≤40% unless contraindicated. • Intravenous β-blockers must be avoided in patients with hypotension or acute heart failure or AV block or severe bradycardia. • Intravenous β-blockers should be considered at the time of presentation in patients undergoing primary PCI without contraindications, with high blood pressure, tachycardia, and no signs of heart failure. • A fasting lipid profile must be obtained in all STEMI patients, as soon as possible after presentation. • It is recommended to initiate or continue high dose statins early after admission in all STEMI patients without contraindication or history of intolerance, regardless of initial cholesterol values and maintain it long-term. • An LDL-C goal of <1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the

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	baseline LDL-C is between 1.8 to 3.5 mmol/L (70 to 135 mg/dL) is recommended. • In patients with LDL-C >1.8 mmol/L (>70 mg/dL) despite a maximally tolerated statin dose who remain at high risk, further therapy to reduce LDL-C should be considered. • ACE inhibitors are indicated starting within the first 24 hours of STEMI in patients with evidence of heart failure, LV systolic dysfunction, diabetes or an anterior infarct. • An ARB, preferably valsartan, is an alternative to ACE inhibitors in patients with heart failure or LV systolic dysfunction, particularly those who are intolerant to ACE inhibitors. • ACE inhibitors should be considered in all patients in the absence of contraindications. • Aldosterone antagonists, e.g. eplerenone, are indicated in patients with an ejection fraction ≤40% and heart failure or diabetes, provided no renal failure or hyperkalemia.
American College of Cardiology/ American Heart Association: **Guideline on the Primary Prevention of Cardiovascular Disease (2019)**[17]	<u>Top 10 messages for the primary prevention of cardiovascular disease</u> • The most important way to prevent atherosclerotic vascular disease, heart failure, and atrial fibrillation is to promote a healthy lifestyle throughout life. • A team-based care approach is an effective strategy for the prevention of cardiovascular disease. Clinicians should evaluate the social determinants of health that affect individuals to inform treatment decisions. • Adults who are 40 to 75 years of age and are being evaluated for cardiovascular disease prevention should undergo 10-year atherosclerotic cardiovascular disease (ASCVD) risk estimation and have a clinician–patient risk discussion before starting on pharmacological therapy, such as antihypertensive therapy, a statin, or aspirin. In addition, assessing for other risk-enhancing factors can help guide decisions about preventive interventions in select individuals, as can coronary artery calcium scanning. • All adults should consume a healthy diet that emphasizes the intake of vegetables, fruits, nuts, whole grains, lean vegetable or animal protein, and fish and minimizes the intake of trans fats, processed meats, refined carbohydrates, and sweetened beverages. For adults with overweight and obesity, counseling and caloric restriction are recommended for achieving and maintaining weight loss. • Adults should engage in at least 150 minutes per week of accumulated moderate-intensity physical activity or 75 minutes per week of vigorous-intensity physical activity. • For adults with type 2 diabetes mellitus, lifestyle changes, such as improving dietary habits and achieving exercise recommendations, are crucial. If medication is indicated, metformin is first-line therapy, followed by consideration of a sodium-glucose cotransporter 2 inhibitor or a glucagon-like peptide-1 receptor agonist. • All adults should be assessed at every healthcare visit for tobacco use, and those who use tobacco should be assisted and strongly advised to quit. • Aspirin should be used infrequently in the routine primary prevention of ASCVD because of lack of net benefit. • Statin therapy is first-line treatment for primary prevention of ASCVD in patients with elevated low-density lipoprotein cholesterol levels (≥190 mg/dL), those with diabetes mellitus, who are 40 to 75 years of age, and those determined to be at sufficient ASCVD risk after a clinician–patient risk discussion. • Nonpharmacological interventions are recommended for all adults with elevated blood pressure or hypertension. For those requiring pharmacological therapy, the target blood pressure should generally be <130/80 mm Hg.

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	Adults with Type 2 Diabetes Mellitus
	• For all adults with T2DM, a tailored nutrition plan focusing on a heart-healthy dietary pattern is recommended to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors.
	• Adults with T2DM should perform at least 150 minutes per week of moderate-intensity physical activity or 75 minutes of vigorous-intensity physical activity to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors.
	• For adults with T2DM, it is reasonable to initiate metformin as first-line therapy along with lifestyle therapies at the time of diagnosis to improve glycemic control and reduce ASCVD risk.
	• For adults with T2DM and additional ASCVD risk factors who require glucose-lowering therapy despite initial lifestyle modifications and metformin, it may be reasonable to initiate a sodium-glucose cotransporter 2 (SGLT-2) inhibitor or a glucagon-like peptide-1 receptor (GLP-1R) agonist to improve glycemic control and reduce CVD risk.
	
	Adults with high blood cholesterol
	• In adults at intermediate risk (≥7.5% to <20% 10-year ASCVD risk), statin therapy reduces risk of ASCVD, and in the context of a risk discussion, if a decision is made for statin therapy, a moderate-intensity statin should be recommended.
	• In intermediate risk (≥7.5% to <20% 10-year ASCVD risk) patients, LDL-C levels should be reduced by 30% or more, and for optimal ASCVD risk reduction, especially in patients at high risk (≥20% 10-year ASCVD risk), levels should be reduced by 50% or more.
	• In adults 40 to 75 years of age with diabetes, regardless of estimated 10-year ASCVD risk, moderate-intensity statin therapy is indicated.
	• In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL (≥4.9 mmol/L) or higher, maximally tolerated statin therapy is recommended.
	• In adults with diabetes mellitus who have multiple ASCVD risk factors, it is reasonable to prescribe high-intensity statin therapy with the aim to reduce LDL-C levels by 50% or more.
	• In intermediate-risk (≥7.5% to <20% 10-year ASCVD risk) adults, risk-enhancing factors favor initiation or intensification of statin therapy.
	• In intermediate-risk (≥7.5% to <20% 10-year ASCVD risk) adults or selected borderline-risk (5% to <7.5% 10-year ASCVD risk) adults in whom a coronary artery calcium score is measured for the purpose of making a treatment decision, AND
	  ○ If the coronary artery calcium score is zero, it is reasonable to withhold statin therapy and reassess in five to 10 years, as long as higher-risk conditions are absent (e.g., diabetes, family history of premature CHD, cigarette smoking);
	  ○ If coronary artery calcium score is one to 99, it is reasonable to initiate statin therapy for patients ≥55 years of age;
	  ○ If coronary artery calcium score is 100 or higher or in the 75th percentile or higher, it is reasonable to initiate statin therapy.
	• In patients at borderline risk (5% to <7.5% 10-year ASCVD risk), in risk discussion, the presence of risk-enhancing factors may justify initiation of moderate-intensity statin therapy.
	
	Adults with high blood pressure or hypertension
	• In adults with elevated blood pressure (BP) or hypertension, including those requiring antihypertensive medications nonpharmacological interventions are recommended to reduce BP. These include:

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	○ weight loss; ○ a heart-healthy dietary pattern; ○ sodium reduction; ○ dietary potassium supplementation; ○ increased physical activity with a structured exercise program; and ○ limited alcohol. • In adults with an estimated 10-year ASCVD risk (ACC/AHA pooled cohort equations to estimate 10-year risk of ASCVD) of 10% or higher and an average systolic BP (SBP) of 130 mm Hg or higher or an average diastolic BP (DBP) of 80 mm Hg or higher, use of BP-lowering medications is recommended for primary prevention of CVD. • In adults with confirmed hypertension and a 10-year ASCVD event risk of 10% or higher, a BP target of less than 130/80 mm Hg is recommended. • In adults with hypertension and chronic kidney disease, treatment to a BP goal of less than 130/80 mm Hg is recommended. • In adults with T2DM and hypertension, antihypertensive drug treatment should be initiated at a BP of 130/80 mm Hg or higher, with a treatment goal of less than 130/80 mm Hg. • In adults with an estimated 10-year ASCVD risk <10% and an SBP of 140 mm Hg or higher or a DBP of 90 mm Hg or higher, initiation and use of BP-lowering medication are recommended. • In adults with confirmed hypertension without additional markers of increased ASCVD risk, a BP target of less than 130/80 mm Hg may be reasonable. <u>Recommendations for treatment of tobacco use</u> • All adults should be assessed at every healthcare visit for tobacco use and their tobacco use status recorded as a vital sign to facilitate tobacco cessation. • To achieve tobacco abstinence, all adults who use tobacco should be firmly advised to quit. • In adults who use tobacco, a combination of behavioral interventions plus pharmacotherapy is recommended to maximize quit rates. • In adults who use tobacco, tobacco abstinence is recommended to reduce ASCVD risk. • To facilitate tobacco cessation, it is reasonable to dedicate trained staff to tobacco treatment in every healthcare system. • All adults and adolescents should avoid secondhand smoke exposure to reduce ASCVD risk. <u>Recommendations for aspirin use</u> • Low-dose aspirin (75 to 100 mg orally daily) might be considered for the primary prevention of ASCVD among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk. • Low-dose aspirin (75 to 100 mg orally daily) should not be administered on a routine basis for the primary prevention of ASCVD among adults >70 years of age. • Low-dose aspirin (75 to 100 mg orally daily) should not be administered for the primary prevention of ASCVD among adults of any age who are at increased risk of bleeding.
American Heart Association/American College of Cardiology/ Heart Failure Society of America: **2022 AHA/ACC**	<u>Treatment of Stage A heart failure (HF)</u> • Hypertension should be controlled in accordance with guideline-directed medication therapy for hypertension to prevent symptomatic HF. (LoE: A) • In patients with type 2 diabetes and either established CVD or at high cardiovascular risk, SGLT-2 inhibitors should be used to prevent hospitalizations for HF. (LoE: A)

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/HFSA Guideline for the Management of Heart Failure (2022)[18]	• In the general population, healthy lifestyle habits such as regular physical activity, maintaining normal weight, healthy dietary patterns, and avoiding smoking are helpful to reduce future risk of HF. (LoE: B) • Patients at risk of developing HF, natriuretic peptide biomarker-based screening followed by team-based care, including a cardiovascular specialist optimizing therapy, can be useful to prevent the development of LV dysfunction (systolic or diastolic) or new-onset HF. (LoE: B) <u>Treatment of Stage B heart failure</u> • In patients with LVEF≤40%, ACE inhibitors should be used to prevent HF and reduce mortality. (LoE: A) • In patients with a recent or remote history of MI or ACS, statins should be used to prevent symptomatic HF and adverse cardiovascular events. (LoE: A) • In patients with a recent MI and LVEF≤40% who are intolerant to ACE inhibitors, ARB should be used to prevent symptomatic HF and reduce mortality. (LoE: B) • In patients with a recent or remote history of MI or ACS and LVEF≤40%, evidence-based beta blockers should be used to reduce mortality. (LoE: B) • In patients who are at least 40 days post-MI with LVEF ≤30% and NYHA class I symptoms while receiving guideline-directed medication therapy and have reasonable expectation of meaningful survival for greater than one year, an implantable cardioverter-defibrillator is recommended for primary prevention of sudden cardiac death to reduce total mortality. (LoE: B) • In patients with LVEF ≤40%, beta blockers should be used to prevent symptomatic HF. (LoE: C) • In patients with LVEF ≤50%, thiazolidinediones should not be used because they increase the risk of HF, including hospitalizations. (LoE: B) • In patients with LVEF ≤50%, nondihydropyridine calcium channel blockers with negative inotropic effects may be harmful. (LoE: C) <u>Treatment for Stage C Heart Failure with Reduced Ejection Fraction (HFrEF)</u> • For patients with stage C HF, avoiding excessive sodium intake is reasonable to reduce congestive symptoms. (LoE: C) • In patients with HF who have fluid retention, diuretics are recommended to relieve congestion, improve symptoms, and prevent worsening HF. (LoE: B) • For patients with HF and congestive symptoms, addition of a thiazide (e.g., metolazone) to treatment with a loop diuretic should be reserved for patients who do not respond to moderate or high dose loop diuretics to minimize electrolyte abnormalities. (LoE: B) • In patients with HFrEF and NYHA class II to III symptoms, the use of an ARNI is recommended to reduce morbidity and mortality. (LoE: A) • In patients with previous or current symptoms of chronic HFrEF, the use of an ACE inhibitor is beneficial to reduce morbidity and mortality when the use of an ARNI is not feasible. (LoE: A) • In patients with previous or current symptoms of chronic HFrEF, who are intolerant to an ACE inhibitor because of cough or angioedema, and when the use of an ARNI is not feasible, the use of an ARB is recommended to reduce morbidity and mortality. (LoE: A) • In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality. (LoE: B) • ARNIs should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor. (LoE: B) • ARNI or ACE inhibitors should not be administered in patients with a history of angioedema. (LoE: C)

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	• In patients with HFrEF, with current or previous symptoms, use of one of the three β-blockers proven to reduce mortality (e.g., bisoprolol, carvedilol, sustained-release metoprolol succinate) is recommended to reduce mortality and hospitalizations. (LoE: A) • In patients with HFrEF and NYHA class II to IV symptoms, a mineralocorticoid receptor antagonist (spironolactone or eplerenone) is recommended to reduce morbidity and mortality, if eGFR is >30 mL/min/1.73 m^2 and serum potassium is <5.0 mEq/L. Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely followed thereafter to minimize risk of hyperkalemia and renal insufficiency. (LoE: A) • In patients taking a mineralocorticoid receptor antagonist whose serum potassium cannot be maintained at <5.5 mEq/L, mineralocorticoid receptor antagonist should be discontinued to avoid life threatening hyperkalemia. (LoE: B) • In patients with symptomatic chronic HFrEF, SGLT-2 an inhibitor is recommended to reduce hospitalization for HF and cardiovascular mortality, irrespective of the presence of type 2 diabetes. (LoE: A) • The combination of hydralazine and isosorbide dinitrate is recommended to improve symptoms and reduce morbidity and mortality for patients self-identified as African Americans with NYHA class III to IV HFrEF receiving optimal therapy. (LoE: A) • In patients with current or previous symptomatic HFrEF who cannot be given first-line agents, such as an ARNI, ACE inhibitor or ARB because of drug intolerance or renal insufficiency, a combination of hydralazine and isosorbide dinitrate might be considered to reduce morbidity and mortality. (LoE: C) • In patients with HF class II to IV symptoms, omega-3 polyunsaturated fatty acid supplementation may be reasonable to use as adjunctive therapy to reduce mortality and cardiovascular hospitalizations. (LoE: B) • In patients with chronic HFrEF without specific indication (e.g., venous thromboembolism, atrial fibrillation, a previous thromboembolic event, or a cardioembolic source, anticoagulation is not recommended. (LoE: B) • Dihydropyridine and non-dihydropyridine calcium channel blockers are not recommended for patients with HFrEF. (LoE: A) • In patients with HFrEF, vitamins, nutritional supplements, and hormonal therapy are not recommended other than to correct specific deficiencies. (LoE: B) • In patients with HFrEF, class IC antiarrhythmic medication and dronedarone may increase risk of mortality. (LoE: A) • In patients with HFrEF, thiazolidinediones increase the risk of worsening HF symptoms and hospitalizations. (LoE: A) • In patients with type 2 diabetes and high cardiovascular risk, the DPP-4 inhibitors, saxagliptin and alogliptin, increase the risk of HF hospitalization and should be avoided in patients with HF. (LoE: B) • In patients with HFrEF, nonsteroidal anti-inflammatory drugs worsen HF symptoms and should be avoided or withdrawn whenever possible. (LoE: B) • For patients with symptomatic (NYHA class II to III) stable chronic HFrEF (LVEF ≤35%) who are receiving guideline-directed medical therapy, including a maximally tolerated dose of a beta blocker, and who are in sinus rhythm with a heart rate of ≥70 beats per minute at rest, ivabradine can be beneficial to reduce HF hospitalizations and cardiovascular death. (LoE: B) • In patients with symptomatic HFrEF despite guideline-directed medical therapy or who are unable to tolerate guideline-directed medical therapy, digoxin might be considered to decrease hospitalizations for HF. (LoE: B) • In select high-risk patients with HFrEF and recent worsening of HF already on guideline-directed medical therapy, an oral soluble guanylate cyclase stimulator (vericiguat) may be considered to reduce HF hospitalization and cardiovascular death. (LoE: B)

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	<u>Pharmacological treatment for Stage C HF with mildly reduced EF and improved EF</u> • In patients with HF with mildly reduced EF, SGLT-2 inhibitors can be beneficial in decreasing HF hospitalizations and cardiovascular mortality. (LoE: B) • Among patients with current or previous symptomatic HF with mildly reduced EF (LVEF, 41 to 49%), use of evidence-based beta blockers for HFrEF, ARNI, ACE inhibitor or ARB, and mineralocorticoid receptor antagonists may be considered to reduce the risk of HF hospitalization and cardiovascular mortality, particularly among patients with LVEF on the lower end of this spectrum. (LoE: B) • In patients with HF with improved EF after treatment, guideline-directed medical therapy should be continued to prevent relapse of HF and LV dysfunction, even in patients who may become asymptomatic. (LoE: B) <u>Pharmacological treatment for Stage C HF with preserved EF (HFpEF)</u> • Patients with hypertension and HFpEF should have medication titrated to attain blood pressure targets in accordance with published clinical practice guidelines to prevent morbidity. (LoE: C) • SGLT-2 inhibitors can be beneficial in decreasing HF hospitalizations and cardiovascular mortality. (LoE: B) • In patients with HFpEF, the use of a mineralocorticoid receptor antagonist, ARB, or ARNI may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum. (LoE: B) • Routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or quality of life in patients with HFpEF is ineffective. (LoE: B) <u>Treatment of Stage D (advanced/refractory) HF</u> • For patients with advanced HF and hyponatremia, the benefit of fluid restriction to reduce congestive symptoms is uncertain. (LoE: C) • Continuous intravenous inotropic support is reasonable as "bridge therapy" in patients with HF (Stage D) refractory to guideline-directed medical therapy and device therapy who are eligible for and awaiting mechanical circulatory support or cardiac transplantation. (LoE: B) • In select patients with HF Stage D, despite optimal guideline-directed medical therapy and device therapy who are ineligible for either mechanical circulatory support or cardiac transplantation, continuous intravenous inotropic support may be considered as palliative therapy for symptom control and improvement in functional status. (LoE: B) • Long-term use of either continuous or intermittent, intravenous inotropic agents, for reasons other than palliative care or as a bridge to advanced therapies, is potentially harmful. (LoE: B)
European Society of Cardiology: **Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (2021)**[19]	<u>Pharmacological treatments indicated in patients with (NYHA Class II-IV) heart failure with reduced ejection fraction</u> • An ACE inhibitor is recommended, in addition to a β-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death. • A mineralocorticoid receptor antagonist (MRA) is recommended for patients with HFrEF, who remain symptomatic despite treatment with an ACE inhibitor and a β-blocker, to reduce the risk of HF hospitalization and death. • Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death. Dapagliflozin or empagliflozin are recommended, in addition to optimal medical therapy with an ACE-I/ARNI, a β-blocker and an MRA, for patients with HFrEF regardless of diabetes status. • Sacubitril-valsartan is recommended as a replacement for an ACE inhibitor to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE

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	inhibitor, a β-blocker, and a mineralocorticoid receptor antagonist. • Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion. • Ivabradine should be considered to reduce the risk of HF hospitalization or cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm despite treatment with an evidence-based dose of β-blocker (or maximum tolerated dose below that), ACE inhibitor (or ARB), and a mineralocorticoid receptor antagonist (or ARB). • Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm who are unable to tolerate or have contraindications for a β-blocker. Patients should also receive an ACE inhibitor (or ARB) and a mineralocorticoid receptor antagonist (or ARB). • An ARB is recommended to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients unable to tolerate an ACE inhibitor (patients should also receive a β-blocker and mineralocorticoid receptor antagonist). • An ARB may be considered to reduce the risk of HF hospitalization and death in patients who are symptomatic despite treatment with a β-blocker who are unable to tolerate a mineralocorticoid receptor antagonist. • Vericiguat may be considered in patients in NYHA class II-IV who have had worsening HF despite treatment with an ACE-I (or ARNI), a β-blocker and an MRA to reduce the risk of CV mortality or HF hospitalization. • Hydralazine and isosorbide dinitrate should be considered in self-identified black patients with LVEF ≤35% or with an LVEF <45% combined with a dilated LV in NYHA Class III–IV despite treatment with an ACE-I a β-blocker and a mineralocorticoid receptor antagonist to reduce the risk of HF hospitalization and death. • Hydralazine and isosorbide dinitrate may be considered in symptomatic patients with HFrEF who can tolerate neither an ACE inhibitor nor an ARB (or they are contraindicated) to reduce the risk of death. • Digoxin is a treatment with less-certain benefits and may be considered in symptomatic patients in sinus rhythm despite treatment with an ACE inhibitor (or ARB), a β-blocker and a mineralocorticoid receptor antagonist, to reduce the risk of hospitalization (both all-cause and HF-hospitalizations). <u>Recommendations for treatment of patients with (NYHA class II-IV) heart failure with mildly reduced ejection fraction (HFmrEF)</u> • Diuretics are recommended in patients with congestion and HFmrEF in order to alleviate symptoms and signs. • An ACE inhibitor may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • An ARB may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • A β-blocker may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • An MRA may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • Sacubitril/valsartan may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. <u>Recommendations for treatment of patients with heart failure with preserved ejection fraction (HFpEF)</u> • It is recommended to screen patients with HFpEF for both cardiovascular and noncardiovascular comorbidities, which, if present, should be treated provided

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	safe and effective interventions exist to improve symptoms, well-being and/or prognosis. • Diuretics are recommended in congested patients with HFpEF in order to alleviate symptoms and signs. <u>Recommendations for the primary prevention of heart failure in patients with risk factors for its development</u> • Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life. • Treatment with statins is recommended in patients at high risk of CV disease or with CV disease in order to prevent or delay the onset of HF, and to prevent HF hospitalizations. • SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with diabetes at high risk of CV disease or with CV disease in order to prevent HF hospitalizations. • Counselling against sedentary habit, obesity, cigarette smoking, and alcohol abuse is recommended to prevent or delay the onset of HF. <u>Recommendations for the initial management of patients with acute heart failure – pharmacotherapy</u> • Intravenous loop diuretics are recommended for all patients with acute HF admitted with signs/symptoms of fluid overload to improve symptoms. It is recommended to regularly monitor symptoms, urine output, renal function and electrolytes during use of intravenous diuretics. • Combination of a loop diuretic with thiazide type diuretic should be considered in patients with resistant oedema who do not respond to an increase in loop diuretic doses. • In patients with acute HF and SBP >110 mmHg, intravenous vasodilators may be considered as initial therapy to improve symptoms and reduce congestion. • Inotropic agents may be considered in patients with SBP <90 mmHg and evidence of hypoperfusion who do not respond to standard treatment, including fluid challenge, to improve peripheral perfusion and maintain end-organ function. • Inotropic agents are not recommended routinely, due to safety concerns, unless the patient has symptomatic hypotension and evidence of hypoperfusion. • A vasopressor, preferably norepinephrine, may be considered in patients with cardiogenic shock to increase blood pressure and vital organ perfusion. • Thromboembolism prophylaxis (e.g. with LMWH) is recommended in patients not already anticoagulated and with no contraindication to anticoagulation, to reduce the risk of deep venous thrombosis and pulmonary embolism. • Routine use of opiates is not recommended, unless in selected patients with severe/intractable pain or anxiety.
Eighth Joint National Committee (JNC 8): **2014 Evidence-based Guideline for the Management of High Blood Pressure in Adults (2014)[20]**	• Pharmacologic treatment should be initiated in patients ≥60 years of age to lower blood pressure at systolic blood pressure ≥150 mm Hg or diastolic blood pressure ≥90 mm Hg and to a goal systolic blood pressure <150 mm Hg and goal diastolic blood pressure <90 mm Hg. Adjustment of treatment is not necessary if treatment results in lower blood pressure and treatment is well tolerated and without adverse effects on health or quality of life. • In patients <60 years of age, pharmacologic treatment should be initiated to lower blood pressure at diastolic blood pressure ≥90 mm Hg to a goal diastolic blood pressure <90 mm Hg. • In patients <60 years of age, pharmacologic treatment should be initiated to lower blood pressure at systolic blood pressure ≥150 mm Hg to a goal diastolic blood pressure <140 mm Hg. • For patients ≥18 years of age with chronic kidney disease or diabetes, pharmacologic treatment should be initiated to lower blood pressure at systolic

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	blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg and to a goal systolic blood pressure <140 mm Hg and goal diastolic blood pressure <90 mm Hg. • Initial antihypertensive treatment for the general nonblack population, including those with diabetes, should include thiazide-type diuretic, calcium channel blocker (CCB), ACE inhibitor, or ARB. • Initial antihypertensive treatment for the general black population, including those with diabetes, should include thiazide-type diuretic or CCB. • For patients ≥18 years of age with chronic kidney disease regardless of race or diabetes status, initial (or add-on) treatment should include an ACE inhibitor or ARB to improve kidney outcomes. • The main goal of antihypertensive treatment is to attain and maintain goal blood pressure. • If goal blood pressure is not attained within a month of treatment, the dose of the initial drug should be increased or second drug from the thiazide-type diuretic, CCB, ACE inhibitor, or ARB classes should be added. • If goal is not achieved with two drugs, a third drug from the thiazide-type diuretic, CCB, ACE inhibitor, or ARB classes should be added. • An ACE inhibitor and ARB should not be used together. • Antihypertensive classes can be used if the patient is unable to achieve goal blood pressure with three agents or had a contraindication to a preferred class. • If blood pressure is not able to be achieved or in complicated patients, referral to a hypertension specialist may be indicated.
International Society of Hypertension: **Global Hypertension Practice Guidelines (2020)**[21]	<u>Lifestyle modifications</u> • Lifestyle modification is the first line of antihypertensive treatment. • Salt reduction: Reduce salt added when preparing foods, and at the table. Avoid or limit consumption of high salt foods such as soy sauce, fast foods and processed food including breads and cereals high in salt. • Healthy diet: Eating a diet that is rich in whole grains, fruits, vegetables, polyunsaturated fats and dairy products and reducing food high in sugar, saturated fat and trans fats, such as the DASH diet. • Healthy drinks: Moderate consumption of coffee, green and black tea. Other beverages that can be beneficial include karkadé (hibiscus) tea, pomegranate juice, beetroot juice and cocoa. • Moderation of alcohol consumption: The recommended daily limit for alcohol consumptions is 2 standard drinks for men and 1.5 for women (10 g alcohol/standard drink). Avoid binge drinking. • Weight reduction: Body weight control is indicated to avoid obesity. Particularly abdominal obesity should be managed. Ethnic-specific cut-offs for BMI and waist circumference should be used. Alternatively, a waist-to-height ratio <0.5 is recommended for all populations. • Smoking cessation: Smoking is a major risk factor for cardiovascular disease (CVD), COPD and cancer. Smoking cessation and referral to smoking cessation programs are advised. • Regular physical activity: Studies suggest that regular aerobic and resistance exercise may be beneficial for both the prevention and treatment of hypertension. Moderate intensity aerobic exercise (walking, jogging, cycling, yoga, or swimming) for 30 minutes on five to seven days per week Strength training also can help reduce blood pressure. Performance of resistance/strength exercises on two to three days per week. • Reduce stress and induce mindfulness: Stress should be reduced and mindfulness or meditation introduced into the daily routine. • Reduce exposure to air pollution and cold temperature: Evidence from studies support a negative effect of air pollution on blood pressure in the long-term.

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	Pharmacological Treatment
	• Ideal characteristics of drug treatment
	  ○ Treatments should be evidence-based in relation to morbidity/mortality prevention.
	  ○ Use a once-daily regimen which provides 24-hour blood pressure control.
	  ○ Treatment should be affordable and/or cost-effective relative to other agents.
	  ○ Treatments should be well-tolerated.
	  ○ Evidence of benefits of use of the medication in populations to which it is to be applied.
	• General scheme for drug treatment
	  ○ Lifestyle modification is the first line of antihypertensive treatment.
	  ○ Grade 1 hypertension (BP 140 to 159/ 90 to 99): Immediate drug treatment in high-risk patients or those with CVD, chronic kidney disease (CKD), diabetes mellitus (DM), or hypertension-mediated organ damage (HMOD). Drug treatment after three to six months of lifestyle intervention if BP still not controlled in low to moderate risk patients.
	  ○ Grade 2 hypertension (BP ≥160/100): Immediate drug treatment in all patients.
	• Core drug-treatment strategy
	  ○ Step 1: Dual low-dose combination (ACE inhibitor or ARB plus dihydropyridine-calcium channel blockers (DHP-CCB)); consider monotherapy in low-risk grade 1 hypertension or in very old (≥80 years) or frail patients; consider ACE/ARB plus thiazide-like diuretic in post-stroke, very elderly, incipient HF, or CCB intolerance; consider ACE/ARB plus DHP-CCB or DHP-CCB plus thiazide-like diuretics in black patients.
	  ○ Step 2: Dual full-dose combination (ACE inhibitor or ARB plus DHP-CCB); consider monotherapy in low-risk grade 1 hypertension or in very old (≥80 years) or frail patients; consider ACE/ARB plus thiazide-like diuretic in post-stroke, very elderly, incipient HF, or CCB intolerance.
	  ○ Step 3: Triple combination (ACE/ARB plus DHP-CCB plus thiazide-like diuretic).
	  ○ Step 4, resistant hypertension: triple combination plus spironolactone or other drug, alternatives include amiloride, doxazosin, eplerenone, clonidine, or β-blocker. Caution with spironolactone or other potassium sparing diuretics when estimated GFR <45 mL/min/1.73m^2 or K+ >4.5 mmol/L.
	  ○ Consider β-blockers at any treatment step when there is a specific indications for their use, e.g., heart failure, angina, post-MI, atrial fibrillation, or younger women planning pregnancy or pregnant.

Hypertension Canada: **2020 Guidelines for the Prevention, Diagnosis, Risk Assessment, and Treatment of Hypertension in Adults and Children (2020)**[22]	Indications for drug therapy for adults with hypertension without compelling indications for specific agents • Antihypertensive therapy should be prescribed for average diastolic blood pressure (DBP) measurements of ≥100 mmHg or average systolic blood pressure (SBP) measurements of ≥160 mmHg in patients without macrovascular target organ damage or other cardiovascular risk factors. • Antihypertensive therapy should be strongly considered for average DPB readings ≥90 mmHg or for average SBP readings ≥140 mmHg in the presence of macrovascular target organ damage or other independent cardiovascular risk factors. • For high-risk patients, aged 50 years or older, with SBP levels ≥130 mmHg, intensive management to target a SBP <120 mmHg should be considered. Patient selection for intensive management is recommended and caution should be taken in certain high-risk groups.

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	Indications for drug therapy for adults with diastolic and with or without systolic hypertension
	• Initial therapy should be with either monotherapy or single pill combination (SPC).
	  ○ Recommended monotherapy choices are:
	  ▪ A thiazide/thiazide-like diuretic, with longer-acting diuretics preferred;
	  ▪ A β-blocker (in patients <60 years of age);
	  ▪ An angiotensin-converting enzyme (ACE) inhibitor (in nonblack patients);
	  ▪ An angiotensin receptor blocker (ARB); or
	  ▪ A long-acting calcium channel blocker (CCB).
	  ○ Recommended SPC choices are those in which an ACE inhibitor is combined with a CCB, ARB with a CCB, or ACE inhibitor or ARB with a diuretic.
	  ○ Hypokalemia should be avoided in patients treated with thiazide/thiazide-like diuretic monotherapy.
	• Additional antihypertensive drugs should be used if target BP levels are not achieved with standard-dose monotherapy. Add-on drugs should be chosen from first-line choices. Useful choices include a thiazide/thiazide-like diuretic or CCB with either: ACE inhibitor, ARB, or β-blocker. Caution should be exercised in combining a nondihydropyridine CCB and a β-blocker. The combination of an ACE inhibitor and an ARB is not recommended.
	• If BP is still not controlled with a combination of two or more first-line agents, or there are adverse effects, other antihypertensive drugs may be added.
	• Possible reasons for poor response to therapy should be considered.
	• α-Blockers are not recommended as first-line agents for uncomplicated hypertension; β-blockers are not recommended as first-line therapy for uncomplicated hypertension in patients ≥60 years of age; and ACE inhibitors are not recommended as first-line therapy for uncomplicated hypertension in black patients. However, these agents may be used in patients with certain comorbid conditions or in combination therapy.
	
	Indications for drug therapy for adults with isolated systolic hypertension
	• Initial therapy should be single-agent therapy with a thiazide/thiazide-like diuretic, a long-acting dihydropyridine CCB, or an ARB. If there are adverse effects, another drug from this group should be substituted. Hypokalemia should be avoided in patients treated with thiazide/thiazide-like diuretic monotherapy.
	• Additional antihypertensive drugs should be used if target BP levels are not achieved with standard-dose monotherapy. Add-on drugs should be chosen from first-line options.
	• If BP is still not controlled with a combination of two or more first-line agents, or there are adverse effects, other classes of drugs (such as α-blockers, ACE inhibitors, centrally acting agents, or nondihydropyridine CCBs) may be combined or substituted.
	• Possible reasons for poor response to therapy should be considered.
	• α-Blockers are not recommended as first-line agents for uncomplicated isolated systolic hypertension; and β-blockers are not recommended as first-line therapy for isolated systolic hypertension in patients ≥60 years of age. However, both agents may be used in patients with certain comorbid conditions or in combination therapy.
	
	Guidelines for hypertensive patients with coronary artery disease (CAD)
	• For most hypertensive patients with CAD, an ACE inhibitor or ARB is recommended.

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	• For hypertensive patients with CAD, but without coexisting systolic heart failure, the combination of an ACE inhibitor and ARB is not recommended.
	• For high-risk hypertensive patients, when combination therapy is being used, choices should be individualized. The combination of an ACE inhibitor and a dihydropyridine CCB is preferable to an ACE inhibitor and a thiazide/thiazide-like diuretic in selected patients.
	• For patients with stable angina pectoris but without previous heart failure, myocardial infarction, or coronary artery bypass surgery, either a β-blocker or CCB can be used as initial therapy.
	• Short-acting nifedipine should not be used.
	• When decreasing SBP to target levels in patients with established CAD (especially if isolated systolic hypertension is present), be cautious when the DBP is ≤60 mmHg because of concerns that myocardial ischemia might be exacerbated, especially in patients with left ventricular hypertrophy (LVH).
	
	<u>Guidelines for patients with hypertension who have had a recent myocardial infarction</u>
	• Initial therapy should include a β-blocker as well as an ACE inhibitor.
	• An ARB can be used if the patient is intolerant of an ACE inhibitor.
	• CCBs may be used in patients after myocardial infarction when β-blockers are contraindicated or not effective. Nondihydropyridine CCBs should not be used when there is heart failure, evidenced by pulmonary congestion on examination or radiography.
	
	<u>Treatment of hypertension in association with heart failure</u>
	• In patients with systolic dysfunction (ejection fraction <40%), ACE inhibitors and β-blockers are recommended for initial therapy. Aldosterone antagonists (mineralocorticoid receptor antagonists) may be combined in treatment for patients with a recent cardiovascular hospitalization, acute myocardial infarction, elevated B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide level, or New York Heart Association (NYHA) Class II-IV symptoms. Careful monitoring for hyperkalemia is recommended when combining an aldosterone antagonist with ACE inhibitor or ARB treatment. Other diuretics are recommended as additional therapy if needed. Beyond considerations of BP control, doses of ACE inhibitors or ARBs should be titrated to those reported to be effective in trials unless adverse effects become manifest.
	• An ARB is recommended if ACE inhibitors are not tolerated.
	• A combination of hydralazine and isosorbide dinitrate is recommended if ACE inhibitors and ARBs are contraindicated or not tolerated.
	• For hypertensive patients whose BP is not controlled, an ARB may be combined with an ACE inhibitor and other antihypertensive drug treatment. Careful monitoring should be used if combining an ACE inhibitor and an ARB because of potential adverse effects such as hypotension, hyperkalemia, and worsening renal function. Additional therapies may also include dihydropyridine CCBs.
	• An angiotensin receptor-neprilysin inhibitor (ARNI) should be used in place of an ACE inhibitor or ARB for patients with HFrEF (<40%) who remain symptomatic despite treatment with appropriate dose of guideline directed HF therapy. Eligible patients must have a serum potassium <5.2 mmol/L, an eGFR ≤30 mL/min/1.73m^2 and close surveillance of serum potassium and creatinine.
	
	<u>Treatment of hypertension in association with stroke</u>
	• BP management in acute ischemic stroke (onset to 72 hours)
	  ○ Please refer to Stroke Best Practice recommendations.
	• BP management after acute ischemic stroke
	  ○ Strong consideration should be given to the initiation of antihypertensive

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	therapy after the acute phase of a stroke or transient ischemic attack. o After the acute phase of a stroke, BP-lowering treatment is recommended to a target of consistently <140/90 mmHg. o Treatment with an ACE inhibitor and thiazide/thiazide-like diuretic combination is preferred. o For patients with stroke, the combination of an ACE inhibitor and ARB is not recommended. • BP management in hemorrhagic stroke (onset to 72 hours) o Please refer to Stroke Best Practice recommendations. <u>Treatment of hypertension in association with LVH</u> • Hypertensive patients with LVH should be treated with antihypertensive therapy to decrease the rate of subsequent cardiovascular events. • The choice of initial therapy can be influenced by the presence of LVH. Initial therapy can be drug treatment using ACE inhibitors, ARBs, long-acting CCBs, or thiazide/thiazide-like diuretics. Direct arterial vasodilators such as hydralazine or minoxidil should not be used. <u>Treatment of hypertension in association with nondiabetic chronic kidney disease</u> • Individualize BP targets in patients with chronic kidney disease. Consider intensive targets (SBP <120 mmHg) in appropriate patients. • For patients with hypertension and proteinuric chronic kidney disease (urinary protein >150 mg per 24 hours or albumin to creatinine ratio >30 mg/mmol), initial therapy should be an ACE inhibitor or an ARB if there is intolerance to ACE inhibitors. • In most cases, combination therapy with other antihypertensive agents might be needed to reach target BP levels. • The combination of an ACE inhibitor and ARB is not recommended for patients with nonproteinuric chronic kidney disease. <u>Treatment of hypertension in association with renovascular disease</u> • Patients with hypertension attributable to atherosclerotic renal artery stenosis should be primarily medically managed because renal angioplasty and stenting offers no benefit over optimal medical therapy alone. • Renal artery angioplasty and stenting for atherosclerotic hemodynamically significant renal artery stenosis could be considered for patients with uncontrolled hypertension resistant to maximally tolerated pharmacotherapy, progressive renal function loss, and acute pulmonary edema. • Patients with confirmed renal fibromuscular dysplasia (FMD) should be referred to a hypertension specialist. • Renal artery angioplasty without stenting is recommended for treatment of FMD-related renal artery stenosis. Stenting is not recommended unless needed because of a periprocedural dissection. Surgical revascularization should be considered in cases of complex lesions less amendable to angioplasty, stenosis associated with complex aneurysm, and restenosis despite two unsuccessful attempts of angioplasty. <u>Treatment of hypertension in association with diabetes mellitus</u> • Persons with diabetes mellitus should be treated to attain SBP of <130 mmHg and DBP of <80 mmHg. • For persons with cardiovascular or kidney disease, including microalbuminuria, or with cardiovascular risk factors in addition to diabetes and hypertension, an ACE inhibitor or an ARB is recommended as initial therapy. • For persons with diabetes and hypertension not included in other guidelines in this section, appropriate choices include (in alphabetical order): ACE inhibitors,

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	ARBs, dihydropyridine CCBs, and thiazide/thiazide-like diuretics. • If target BP levels are not achieved with standard-dose monotherapy, additional antihypertensive therapy should be used. For persons in whom combination therapy with an ACE inhibitor is being considered, a dihydropyridine CCB is preferable to a thiazide/thiazide-like diuretic. <u>Resistant hypertension</u> • Resistant hypertension is defined as BP above target despite three or more BP-lowering drugs at optimal doses preferably including a diuretic (and usually a renin-angiotensin-aldosterone system blocker and a CCB. • Accurate office and out-of-office BP measurement is essential. • Other reasons for apparent resistant hypertension should be eliminated before diagnosing true resistant hypertension, including nonadherence, white coat effect, and secondary hypertension. • Pharmacotherapy with the additional use of spironolactone, bisoprolol, doxazosin, amiloride, eplerenone, or clonidine with the baseline regimen decreases BP significantly, with the greatest BP-lowering shown with spironolactone. • Patients with resistant hypertension should be referred to providers with expertise in diagnosis and management of hypertension. <u>Hypertension and pediatrics</u> • BP should be measured regularly in children three years of age or older; the auscultatory method is the gold-standard at present. • Initial therapy should be monotherapy, with an ACE inhibitor or ARB (not first-line in black children), or a long-acting dihydropyridine CCB. • The treatment t goal is systolic and diastolic office BP and/or ABPM < 95th percentile or <90th percentile in children with risk factors or target organ damage. • Complex cases should be referred to an expert in pediatric hypertension. <u>Hypertension and pregnancy</u> • Up to 7% of pregnancies are complicated by a hypertensive disorder of pregnancy, and approximately 5% of women will have chronic hypertension when they become pregnant. • The prevalence of hypertension in pregnancy is expected to increase with women becoming pregnant later in their reproductive years and the increasing prevalence of cardiovascular comorbidities such as increased preconception body mass index and maternal diabetes. • The possibility of pregnancy should be considered when managing women with hypertension who are of reproductive age. • Preconception counselling should be offered to all women with hypertension who are considering pregnancy. • ACE inhibitor and ARB therapy should be avoided before conception and during pregnancy unless there is a compelling indication for their use (i.e., proteinuric kidney disease). • Hypertension during pregnancy can increase the risk of adverse maternal and fetal outcomes, including an increased risk of preeclampsia, placental abruption, prematurity, small for gestational age infants, stillbirth, and maternal renal and retinal injury, thus generally requires involvement of an interdisciplinary team including obstetrical care providers. • Antihypertensive therapy is recommended for average SBP measurements of ≥140 mmHg or DBP measurements of ≥90 mmHg in pregnant women with chronic hypertension, gestational hypertension, or preeclampsia. Initial antihypertensive therapy should be monotherapy from the following first-line drugs: oral labetalol, oral methyldopa, long-acting oral nifedipine, or other oral

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	b-blockers (acebutolol, metoprolol, pindolol, and propranolol). Other antihypertensive drugs can be considered as second-line drugs including: clonidine, hydralazine, and thiazide diuretics. • Women with severe hypertension with SBP ≥160 mmHg or DBP ≥110 mmHg in pregnancy or postpartum require urgent antihypertensive therapy because it is considered an obstetrical emergency. • Antihypertensive drugs used in breastfeeding women include: labetalol, methyldopa, long-acting nifedipine, enalapril, or captopril.
European Society of Hypertension: **2023 Guidelines for the management of arterial hypertension (2023)**[23]	General recommendations for antihypertensive drug treatment • BP lowering should be prioritized over the selection of specific antihypertensive drug classes because treatment benefit largely originates from BP reduction. • Five major drug classes including, ACE inhibitors, ARBs, β-blockers, CCBs, and Thiazide/Thiazide-like diuretics have effectively reduced blood pressure and cardiovascular events in randomized controlled trials. These drugs and their combinations are recommended as the basis of antihypertensive treatment strategies. • Initiation of therapy with a two-drug combination is recommended for most hypertensive patients. Preferred combinations should comprise a RAS blocker (either an ACE inhibitor or an ARB) with a CCB or thiazide/thiazide-like diuretic. Other combinations of the five major drug classes can be used. • Initiation with monotherapy can be considered in patients with: grade 1 hypertension and low-risk if BP is only marginally elevated (less than 150 mmHg SBP and 95 mmHg DBP) high-normal BP and very high cardiovascular risk, frailty and/or and advance age. • If BP is not controlled with the initial two-drug combination by using the maximum recommended and tolerated dose of the respective components, treatment should be increased to a three-drug combination, usually a RAS blocker plus CCB plus thiazide/thiazide-like diuretic. • If BP is not controlled with a three-drug combination by using the maximum recommended and tolerated dose of the respective components, it is recommended to extend treatment according to the recommendations for resistant hypertension. • The use of single pill combinations should be preferred at any treatment step (i.e. during initiation of therapy with a two-drug combination and at any other step of treatment). • β-blocker should be used at initiation of therapy or at any treatment step as guideline-directed medical therapy (e.g., heart failure with reduced ejection fraction, anti-ischemic therapy in chronic coronary syndromes, heart rate control in atrial fibrillation). • β-blockers can be considered in the presence of several other conditions in which their use can be favorable. • The combination of two RAS blockers is not recommended due to increased risk of adverse events, in particular AKI. True-resistant hypertension • In resistant hypertension, it is recommended to reinforce lifestyle measures. • Drugs that can be considered as additional therapy in patients with resistant hypertension are preferably spironolactone (or other MRA), or β-blocker or Alpha-1 blockers or centrally acting agents (clonidine), or amiloride. • Thiazide/thiazide-like diuretics are recommended in resistant hypertension if estimated eGFR is ≥30 mL/min/1.73m^2. • Loop diuretics may be considered in patients with an estimated eGFR < 45 mL/min/1.73m^2 and should be used if eGFR falls below 30 mL/min/1.73m^2. • Chlorthalidone (12.5 to 25 mg once daily) could be used with or without a loop diuretic if eGFR is <30 mL/min/1.73m^2.

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	• Renal deprivation can be considered as an additional treatment option in patients with resistant hypertension if eGFR is >40 mL/min/1.73m^2. • Patients with resistant hypertension should be followed very closely. Follow-up includes periodical ambulatory blood pressure monitoring and assessment of hypertension-mediated organ damage, particularly kidney function and serum potassium levels. Regular use of home blood pressure monitoring and monitoring of drug adherence are desirable.
National Institute for Health and Clinical Excellence: **Hypertension in adults: diagnosis and management (2019)**[24]	<u>Choosing antihypertensive drug treatment (for people with or without type II diabetes)</u> • Where possible, recommend treatment with drugs taken only once a day. • Prescribe non-proprietary drugs where these are appropriate and minimize cost. • Offer people with isolated systolic hypertension (systolic blood pressure ≥160 mmHg) the same treatment as people with both raised systolic and diastolic blood pressure. • Offer antihypertensive drug treatment to women of child-bearing potential with diagnosed hypertension in line with recommendations in this guideline. For women considering pregnancy or who are pregnant or breastfeeding, manage hypertension in line with the recommendations on Management of pregnancy with chronic hypertension and Breastfeeding in 'Hypertension in pregnancy'. • When choosing antihypertensive drug treatment for adults of black African or African-Caribbean family origin, consider an angiotensin II receptor blocker, in preference to an angiotensin-converting enzyme inhibitor. <u>Step one treatment</u> • Patients <55 years of age should be offered a step one antihypertensive with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). • Offer an ACE inhibitor or an ARB to adults starting step 1 antihypertensive treatment who have type II diabetes and are of any age or family origin or those aged <55 years but not of black African or African-Caribbean family origin. • If an ACE inhibitor is not tolerated, offer an ARB. • Do not combine an ACE inhibitor with an ARB for the treatment of hypertension. • Offer a calcium channel blocker (CCB) to adults starting step 1 antihypertensive treatment who are >55 years of age and do not have diabetes and are of black African or African-Caribbean family origin and do not have type II diabetes and of any age. • If a CCB is not suitable, for example because of edema or intolerance, or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic. • If diuretic treatment is to be initiated or changed, offer a thiazide‑like diuretic, such as indapamide in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide. • For adults with hypertension who are already receiving treatment with bendroflumethiazide or hydrochlorothiazide, who have stable, well-controlled blood pressure, continue with their treatment. <u>Step two treatment</u> • Before considering next step treatment for hypertension discuss with the person if they are taking their medicine as prescribed and support adherence in line with NICE's guideline on “Medicines adherence: involving patients decisions about prescribed medicines and supporting adherence”. • If hypertension is not controlled with a step one treatment of an ACE inhibitor or ARB, offer choice of one of the following drugs in addition to the step one treatment: a CCB or a thiazide-like diuretic.

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	• If hypertension is not controlled in adults taking step one treatment of a CCB, offer the choice of one of the following drugs in addition to the step one treatment: an ACE inhibitor or an ARB or a thiazide-like diuretic. • If hypertension is not controlled in adults of black African or African–Caribbean family origin who do not have type 2 diabetes taking step one treatment, consider an ARB, in preference to an ACE inhibitor, in addition to step one treatment. <u>Step three treatment</u> • Before considering step three treatment, review the person's medications to ensure they are being taken at the optimal doses and discuss adherence (see recommendation under step two). • If hypertension is not controlled in adults taking step two treatment, offer a combination of an ACE inhibitor or ARB and a CCB and a thiazide-like diuretic. <u>Step four treatment</u> • If hypertension is not controlled in adults taking the optimal tolerated doses of an ACE inhibitor or an ARB plus a CCB and a thiazide-like diuretic, regard them as having resistant hypertension. • Before considering further treatment for a person with resistant hypertension, confirm elevated clinic blood pressure measurements using ambulatory or home blood pressure recordings, assess for postural hypotension, and discuss adherence. • For people with confirmed resistant hypertension, consider adding a fourth antihypertensive drug as step four treatment or seeking specialist advice. • Consider further diuretic therapy with low-dose spironolactone for adults with resistant hypertension starting step four treatment who have a blood potassium level of 4.5 mmol/l or less. Use particular caution in people with a reduced estimated glomerular filtration rate because they have an increased risk of hyperkalemia. • When using further diuretic therapy for step four treatment of resistant hypertension, monitor blood sodium and potassium and renal function within one month of starting treatment and repeat as needed thereafter. • Consider an alpha-blocker or beta-blocker for adults with resistant hypertension starting step four treatment who have a blood potassium level of more than 4.5 mmol/l. • If blood pressure remains uncontrolled in people with resistant hypertension taking the optimal tolerated doses of four drugs, seek specialist advice.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in Blacks (2010)**[25]	• To attain and maintain blood pressure (BP) below target levels, multiple antihypertensive drugs will be required in most hypertensive blacks. • Use of two-drug combination therapy when SBP is >15 mm Hg and/or DBP is >10 mm Hg above goal levels is increasingly recommended as first-line therapy. • Two-drug regimens have generally contained a thiazide-type diuretic; however, the combination of a calcium channel blocker (CCB) with either an ACE inhibitor or an ARB has been shown equally efficacious in BP lowering but with demonstrated superiority (CCB+ACE) for hard clinical outcomes compared with the same ACE inhibitor plus a thiazide-type diuretic. • In secondary prevention patients, the combination therapy should include a drug(s) with the appropriate compelling indications. • Certain classes of antihypertensive medications, specifically diuretics and CCBs, lower BP on average more than β-blockers and renin-angiotensin system (RAS) blockers in black patients when used as monotherapies. • In the absence of compelling indications, when BP is near goal levels, monotherapy with a diuretic or a CCB is preferred. • Lifestyle modifications should be initiated in all patients with hypertension, whether or not pharmacotherapy is planned.

Clinical Guideline	Recommendations
	• ACE inhibitors or ARBs are recommended as alternative monotherapy options in the treatment of hypertension in blacks. The rationale for their lower tier monotherapy recommendation is because they have consistently achieved lesser average reductions in BP relative to that observed with monotherapy using either a diuretic or CCB.
Kidney Disease Improving Clinical Outcomes Group: **KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease (2021)**[26]	<u>Blood pressure measurement</u> • The Work Group recommends standardized office blood pressure (BP) measurement in preference to routine office BP measurements for the management of high BP in adults. • The Work Group suggests that out-of-office BP measurements with ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM) be used to complement standardized office BP readings for the management of high BP. <u>Lifestyle interventions for lowering BP in patients with chronic kidney disease (CKD) not receiving dialysis</u> • The Work Group suggests targeting a sodium intake <2 grams of sodium per day (or <90 mmol of sodium per day, or <5 grams of sodium chloride per day) in patients with high BP and CKD. • The Work Group suggests that patients with high BP and CKD be advised to undertake moderate-intensity physical activity for a cumulative duration of at least 150 minutes per week, or to a level compatible with their cardiovascular and physical tolerance. <u>BP management in patients with CKD, with or without diabetes, not receiving dialysis</u> • The Work Group suggests that adults with high BP and CKD be treated with a target systolic BP (SBP) of <120 mmHg, when tolerated, using standardized office BP measurement. • The Work Group recommends starting renin-angiotensin-system inhibitors (RASi) (angiotensin-converting enzyme inhibitor [ACEi] or angiotensin II receptor blocker [ARB]) for people with high BP, CKD, and severely increased albuminuria without diabetes. • The Work Group suggests starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately increased albuminuria without diabetes. • The Work Group recommends starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately-to-severely increased albuminuria with diabetes. • The Work Group recommends avoiding any combination of ACEi, ARB, and direct renin inhibitor (DRI) therapy in patients with CKD, with or without diabetes. <u>BP management in kidney transplant recipients</u> • Treat adult kidney transplant recipients with high BP to a target BP of <130 mmHg systolic and <80 mmHg diastolic using standardized office BP measurement. • The Work Group recommends that a dihydropyridine calcium channel blocker (CCB) or an ARB be used as the first-line antihypertensive agent in adult kidney transplant recipients. <u>BP management in children with CKD</u> • The Work Group suggests that in children with CKD, 24-hour mean arterial pressure by ABPM should be lowered to <50th percentile for age, sex, and height.
American College of Cardiology/ American Heart Association Task Force:	<u>Initiation of Blood Pressure (BP) Treatment for Overall Cardiovascular Disease (CVD) Risk</u> • Use of BP-lowering medications is recommended for secondary prevention of recurrent CVD events in patients with clinical CVD and an average systolic

Clinical Guideline	Recommendations
Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults (2017)[27]	blood pressure (SBP) ≥130 mmHg or an average diastolic blood pressure (DBP) of ≥80 mmHg and for primary prevention in adults with an estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk of ≥10% and an average SBP of ≥130 mmHg or an average ≥80 mmHg. • Use of BP-lowering medication is recommended for primary prevention of CVD in adults with no history of CVD and with an estimated 10-year ASCVD risk <10% and an SBP of ≥140 mmHg or a DBP of ≥90 mmHg. • Simultaneous use of an angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), and/or renin inhibitor is potentially harmful and is not recommended to treat adults with hypertension. • For adults with confirmed hypertension and known CVD or 10-year ASCVD risk of ≥10%, a BP target <130/80 mmHg is recommended. For adults with confirmed hypertension without additional markers of increased CVD risk, a BP target <130/80 mmHg may be reasonable. • For initiation of antihypertensive drug therapy, first-line agents include thiazide diuretics, calcium channel blockers (CCBs), and ACE inhibitors or ARBs. • Initiation of antihypertensive drug therapy with two first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended in adults with stage 2 hypertension and an average BP >20/10 mmHg above their BP target. • Initiation of antihypertensive drug therapy with a single antihypertensive drug is reasonable in adults with stage 1 hypertension and BP goal <130/80 mmHg with dosage titration and sequential addition of other agents to achieve the BP target. <u>Stable Ischemic Heart Disease (SIHD)</u> • In adults with SIHD and hypertension, a BP target <130/80 is recommended. • Adults with SIHD and hypertension (BP ≥130/80 mmHg) should be treated with medications [e.g., guideline-directed medical therapy (GDMT) beta-blockers, ACE inhibitors, or ARBs] for compelling indications [e.g., previous myocardial infarction (MI), stable angina] as first-line therapy, with the addition of other drugs (e.g., dihydropyridine CCBs, thiazide diuretics, and/or mineralocorticoid receptor antagonists) as needed to further control hypertension. • In adults with SIHD with angina and persistent uncontrolled hypertension, the addition of dihydropyridine CCBs to GDMT beta-blockers is recommended. • In adults who have had a MI or acute coronary syndrome, it is reasonable to continue GDMT beta-blockers beyond three years as long-term therapy for hypertension. • Beta-blockers and/or CCBs might be considered to control hypertension in patients with coronary artery disease (CAD) had an MI more than three years ago and have angina. <u>Heart Failure</u> • In adults with increased risk of HF, the optimal BP in those with hypertension should be <130 mmHg. • Adults with HFrEF and hypertension should be prescribed GDMT titrated to attain a BP <130/80 mmHg. • Non-dihydropyridine CCBs are not recommended in the treatment of hypertension in adults with HFrEF. • In adults with HFpEF who present with symptoms of volume overload, diuretics should be prescribed to control hypertension. • Adults with HFpEF and persistent hypertension after management of volume overload should be prescribed ACE inhibitors or ARBs and beta-blockers titrated to attain SBP <130 mmHg. <u>CKD</u>

Clinical Guideline	Recommendations
	• Adults with hypertension and CKD should be treated to a BP goal <130/80 mmHg. • In adults with hypertension and CKD [stage 3 or higher or stage 1 or 2 with albuminuria (≥300 mg/d, or ≥300 mg/g albumin-to-creatinine ratio or the equivalent in the first morning void)], treatment with an ACE inhibitor is reasonable to slow kidney disease progression. Treatment with an ARB may be reasonable if an ACE inhibitor is not tolerated. • After kidney transplantation, it is reasonable to treat patients with hypertension to a BP goal <130/80 mmHg and with a CCB on the basis of improved glomerular filtration rate (GFR) and kidney survival. Cerebrovascular Disease • In adults with intracerebral hemorrhage (ICH) who present with SBP >220 mmHg, it is reasonable to use continuous intravenous (IV) drug infusion and close BP monitoring to lower levels. Immediate lowering of SBP to <140 mmHg in adults with spontaneous ICH who present within six hours of the acute event and have an SBP between 150 mmHg and 220 mmHg is not of benefit to reduce death or severe disability and can be potentially harmful. • Adults with acute ischemic stroke and elevated BP who are eligible for treatment with IV tissue plasminogen activator (tPA) should have their BP slowly lowered to <185/110 mmHg before thrombolytic therapy is initiated. • In adults with an acute ischemic stroke, BP should be <185/110 mmHg before administration of IV tPA and should be maintained below 180/105 mmHg for at least the first 24 hours after initiation drug therapy. • Starting or restarting antihypertensive therapy during hospitalization in patients with BP >140/90 mmHg who are neurologically stable is safe and reasonable to improve long-term BP control, unless contraindicated. • In patient with BP ≥220/120 mmHg who did not receive IV alteplase or endovascular treatment and have no comorbid conditions requiring acute antihypertensive treatment, the benefit of initiating or reinitiating treatment of hypertension within the first 48 to 72 hours is uncertain. It might be reasonable to lower BP by 15% during the first 24 hours after onset of stroke. In patients with BP <220/120 mmHg with the same conditions, initiating or reinitiating treatment of hypertension within the first 48 to 72 hours after an acute ischemic stroke is not effective to prevent death or dependency. • Adults with previously treated stroke or transient ischemic attack should be restarted on antihypertensive treatment after the first few days of the index event to reduce the risk of recurrent stroke and other vascular events. Treatment with a thiazide diuretic, ACE inhibitor, or ARB, or combination treatment consisting of a thiazide diuretic plus ACE inhibitor, is useful. • Adults not previously treated for hypertension who experienced a stroke or transient ischemic attack and have an established BP ≥140/90 mmHg should be prescribed antihypertensive treatment a few days after the index event to reduce the risk of recurrent stroke and other vascular event. • For adults who experience a stroke or transient ischemic attack, selection of specific drugs should be individualized on the basis of patient comorbidities and agent pharmacological class. • For adults who experience a stroke or transient ischemic attack, a BP goal <130/80 mmHg may be reasonable. • For adults with a lacunar stroke, a target SBP goal <130 mmHg may be reasonable. • In adults previously untreated for hypertension who experience an ischemic stroke or transient ischemic attack and have an SBP <140 mmHg and a DBP <90 mmHg, the usefulness of initiating antihypertensive treatment is not well established.

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	Peripheral Artery Disease (PAD) • Adults with hypertension and PAD should be treated similarly to patients with hypertension without PAD. Diabetes Mellitus (DM) • In adults with DM and hypertension, antihypertensive drug treatment should be initiated at a BP of ≥130/80 mmHg with a treatment goal <130/80 mmHg. • In adults with DM and hypertension, all first-line classes of antihypertensive agents (i.e., diuretics, ACE inhibitors, ARBs, and CCBs) are useful and effective. • In adults with DM and hypertension, ACE inhibitors or ARBs may be considered in the presence of albuminuria. Atrial Fibrillation, Valvular Heart Disease, and Aortic disease • Treatment of hypertension can be useful for prevention of recurrence of AF. • In adults with asymptomatic aortic stenosis, hypertension should be treated with pharmacotherapy, starting at a low dose and gradually titrating upward as needed. • In patients with chronic aortic insufficiency, treatment of systolic hypertension with agents that do not slow the heart rate (i.e., avoid beta-blockers) is reasonable. • Beta-blockers are recommended as the preferred antihypertensive agents in patients with hypertension and thoracic aortic disease. Racial and Ethnic Differences in Treatment • In black adults with hypertension but without HF or CKD, including those with DM, initial antihypertensive treatment should include a thiazide-type diuretic or CCB. Two or more antihypertensive medications are recommended to achieve a BP target <130/80 mmHg in most adults with hypertension, especially in black adults with hypertension. Pregnancy • Women with hypertension who become pregnant, or are planning to become pregnant, should be transitioned to methyldopa, nifedipine, and/or labetalol during pregnancy. • Women with hypertension who become pregnant should not be treated with ACE inhibitors, ARBs, or direct renin inhibitors. Older Persons • Treatment of hypertension with an SBP treatment goal <130 mmHg is recommended for noninstitutionalized ambulatory community-dwelling adults (≥65 years of age) with an average SBP of ≥130 mmHg. • For older adults (≥65 years of age) with hypertension and a higher burden of comorbidity and limited life expectancy, clinical judgment, patient preference, and a team-based approach to assess risk/benefit is reasonable for decisions regarding intensity of BP lowering and choice of antihypertensive drugs. Hypertensive Crises • In adults with a hypertensive emergency, admission to an intensive care unit is recommended for continuous monitoring of BP and target organ damage and for parenteral administration of an appropriate agent. • For adults with a compelling condition (i.e., aortic dissection, severe pre-eclampsia or eclampsia, or pheochromocytoma crisis), SBP should be reduced to <140 mmHg during the first hour and to <120 mmHg in aortic dissection. • For adults without a compelling condition, SBP should be reduced by no more than 25% within the first hours; then, if stable, to 160/100 mmHg within the next

Clinical Guideline	Recommendations
	two to six hours; and then cautiously to normal during the following 24 to 48 hours. Cognitive Decline and Dementia • In adults with hypertension, BP lowering is reasonable to prevent cognitive decline and dementia. Patients Undergoing Surgical Procedures • In patients with hypertension undergoing major surgery who have been on beta-blockers chronically, beta-blockers should be continued. • In patients with hypertension undergoing planned elective major surgery, it is reasonable to continue medical therapy for hypertension until surgery. • In patients with hypertension undergoing major surgery, discontinuation of ACE inhibitors or ARBs perioperatively may be considered. • In patients with planned elective major surgery and SBP ≥180 mmHg or DBP ≥110 mmHg, deferring surgery may be considered. • For patients undergoing surgery, abrupt pre-operative discontinuation of beta-blockers or clonidine is potentially harmful. • Beta-blockers should not be started on the day of surgery in beta-blocker-naïve patients. • Patients with intraoperative hypertension should be managed with IV medications until such time as oral medications can be resumed.
American Diabetes Association: **Standards of Medical Care in Diabetes (2023)**[28]	Hypertension/blood pressure control • Blood pressure should be measured at every routine visit. When possible, patients found to have elevated blood pressure (systolic blood pressure 120 to 129 mmHg and diastolic <80 mmHg) should have blood pressure confirmed using multiple readings, including measurements on a separate day, to diagnose hypertension. Patients with blood pressure ≥180/110 and cardiovascular disease could be diagnosed with hypertension at a single visit. • All hypertensive patients with diabetes should monitor their blood pressure at home. • For patients with diabetes and hypertension, blood pressure targets should be individualized through a shared decision-making process that addresses cardiovascular risk, potential adverse effects of antihypertensive medications, and patient preferences. • Individuals with diabetes and hypertension qualify for antihypertensive drug therapy when the blood pressure is persistently elevated ≥130/80 mmHg. The on-treatment target blood pressure goal is <130/80 mmHg, if it can be safely attained. • In pregnant patients with diabetes and preexisting hypertension, a blood pressure target of 110 to 135/85 is suggested in the interest of reducing the risk for accelerated maternal hypertension and minimizing impaired fetal growth. • For patients with blood pressure >120/80, lifestyle intervention consists of weight loss when indicated, a Dietary Approaches to Stop Hypertension (DASH)-style eating pattern including reducing sodium and increasing potassium intake, moderation of alcohol intake, and increased physical activity. • Patients with confirmed office-based blood pressure ≥130/80 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of pharmacologic therapy to achieve blood pressure goals. • Patients with confirmed office-based blood pressure ≥160/100 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of two drugs or a single pill combination of drugs demonstrated to reduce cardiovascular events in patients with diabetes. • Treatment for hypertension should include drug classes demonstrated to reduce cardiovascular events in patients with diabetes (ACE inhibitors, angiotensin

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	receptor blockers, thiazide-like diuretics, or dihydropyridine calcium channel blockers). ACE inhibitors or angiotensin receptor blockers are recommended first-line therapy for hypertension in people with diabetes and coronary artery disease. • Multiple-drug therapy is generally required to achieve blood pressure targets (but not a combination of ACE inhibitors and angiotensin receptor blockers). • An ACE inhibitor or angiotensin receptor blocker, at the maximum tolerated dose indicated for blood pressure treatment, is the recommended first-line treatment for hypertension in patients with diabetes and urinary albumin–to–creatinine ratio ≥300 mg/g creatinine or 30 to 299 mg/g creatinine. If one class is not tolerated, the other should be substituted. • For patients treated with an ACE inhibitor, angiotensin receptor blocker, or diuretic, serum creatinine/estimated glomerular filtration rate and serum potassium levels should be monitored at least annually. • Patients with hypertension who are not meeting blood pressure targets on three classes of antihypertensive medications (including a diuretic) should be considered for mineralocorticoid receptor antagonist therapy. <u>Chronic kidney disease</u> • At least once a year, assess urinary albumin (e.g., spot urinary albumin–to–creatinine ratio) and estimated glomerular filtration rate in patients with type 1 diabetes with duration of five or more years and in all patients with type 2 diabetes. • In people with established diabetic kidney disease, urinary albumin (e.g., spot urinary albumin-to-creatinine ratio) and estimated glomerular filtration rate should be monitored one to four times per year depending on the stage of the disease. Optimize glucose control to reduce the risk or slow the progression of chronic kidney disease (CKD). • For patients with type 2 diabetes and diabetic kidney disease, use of a sodium-glucose cotransporter 2 inhibitor in patients with an estimated glomerular filtration rate ≥20 mL/min/1.73 m^2 and urinary albumin ≥200 mg/g creatinine is recommended to reduce CKD progression and cardiovascular events. • For patients with type 2 diabetes and diabetic kidney disease, use of a sodium–glucose cotransporter 2 inhibitor is recommended to reduce chronic kidney disease progression and cardiovascular events in patients with an estimated glomerular filtration rate ≥20 mL/min/1.73 m^2 and urinary albumin ranging from normal to 200 mg/g creatinine. • In people with type 2 diabetes and diabetic kidney disease, consider use of sodium–glucose cotransporter 2 inhibitors (if estimated glomerular filtration rate is ≥20 mL/min/1.73 m^2), a glucagon-like peptide 1 agonist, or a nonsteroidal mineralocorticoid receptor antagonist (if estimated glomerular filtration rate is ≥25 mL/min/1.73 m^2) additionally for cardiovascular risk reduction. • In people with chronic kidney disease and albuminuria who are at increased risk for cardiovascular events or chronic kidney disease progression, a nonsteroidal mineralocorticoid receptor antagonist shown to be effective in clinical trials is recommended to reduce chronic kidney disease progression and cardiovascular events. • Optimize blood pressure control and reduce blood pressure variability to reduce the risk or slow the progression of CKD. • Do not discontinue renin-angiotensin system blockade for minor increases in serum creatinine (≤30%) in the absence of volume depletion. • For people with nondialysis-dependent stage 3 or higher CKD, dietary protein intake should be a maximum of 0.8 g/kg body weight per day (the recommended daily allowance). For patients on dialysis, higher levels of dietary protein intake should be considered, since protein energy wasting is a major problem in some

Clinical Guideline	Recommendations
	dialysis patients. • In nonpregnant patients with diabetes and hypertension, either an ACE inhibitor or an angiotensin receptor blocker is recommended for those with modestly elevated urinary albumin–to–creatinine ratio (30 to 299 mg/g creatinine) and is strongly recommended for those with urinary albumin–to–creatinine ratio ≥300 mg/g creatinine and/or estimated glomerular filtration rate <60 mL/min/1.73 m^2. • Periodically monitor serum creatinine and potassium levels for the development of increased creatinine and hyperkalemia when ACE inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists are used, or hypokalemia when diuretics are used. • An ACE inhibitor or an angiotensin receptor blocker is not recommended for the primary prevention of CKD in patients with diabetes who have normal blood pressure, normal urinary albumin–to–creatinine ratio (<30 mg/g creatinine), and normal estimated glomerular filtration rate. • Patients should be referred for evaluation by a nephrologist if they have continuously increasing urinary albumin levels and/or continuously decreasing estimated glomerular filtration rate and an estimated glomerular filtration rate <30 mL/min/1.73 m^2. • Promptly refer to a nephrologist for uncertainty about the etiology of kidney disease, difficult management issues, and rapidly progressing kidney disease.
American Association for the Study of Liver Diseases: **Diagnosis, Evaluation, and Management of Ascites, Spontaneous Bacterial Peritonitis and Hepatorenal Syndrome: 2021 Practice Guidance (2021)**[29]	Treatment of ascites • Moderate sodium restriction (2 g or 90 mmol/day) and diuretics (spironolactone with or without furosemide) are the first-line treatment in patients with cirrhosis and grade 2 ascites. • After ascites is adequately mobilized, attempts should be made to taper the diuretics to the lowest dose necessary to maintain minimal or no ascites to prevent the development of adverse effects. • Fluid restriction is not necessary unless serum sodium is <125 mmol/L. • In patients receiving diuretics, body weight and serum creatinine and sodium should be regularly monitored to assess response and to detect the development of adverse effects. • Human albumin solution (20 to 40 g/week) or baclofen administration (10 mg/day, with a weekly increase of 10 mg/day, up to 30 mg/day) can be considered in cases of severe muscle cramps. • Large-volume paracentesis is the first-line treatment of grade 3 ascites. After paracentesis, sodium restriction and diuretics should be started. • Referral for liver transplant evaluation should be considered in patients with grade 2 or 3 ascites. • Nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers should be avoided in patients with cirrhosis and ascites. • Aminoglycosides should be avoided whenever possible in the treatment of bacterial infections. • For patients with cirrhosis and diuretic-responsive ascites, controversial data suggest potential benefits of long-term infusion of human albumin solution. At present, no recommendation can be made for its use in routine clinical practice.
Endocrine Society: **The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment (2016)**[30]	• Unilateral laparoscopic adrenalectomy is recommended for patients with documented unilateral primary aldosteronism (i.e., aldosterone-producing adenoma [APA] or unilateral adrenal hyperplasia [UAH]). If a patient is unable or unwilling to undergo surgery, medical treatment including a mineralocorticoid receptor (MR) antagonist is recommended. If an aldosterone to renin ratio (ARR)-positive patient is unwilling or unable to undergo further investigations, medical treatment including an MR antagonist is recommended.

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	• In patients with primary aldosteronism due to bilateral adrenal disease, medical treatment with an MR antagonist is recommended; spironolactone is suggested as the primary agent, with eplerenone as an alternative • In patients with glucocorticoid remediable aldosteronism (GRA), administering the lowest dose of glucocorticoid to lower adrenocorticotropic hormone (ACTH) and thus normalize BP and potassium levels is recommended as the first-line treatment. In addition, if BP fails to normalize with glucocorticoid alone, an MR antagonist may be added. For children, the glucocorticoid dosage should be adjusted for age and body weight, and BP targets should be determined from age- and gender-specific published normative data.

*Agent not available in the United States.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the mineralocorticoid (aldosterone) receptor antagonists are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Mineralocorticoid (Aldosterone) Receptor Antagonists[1-7]

Indication(s)	Single Entity Agents			Combination Products
	Eplerenone	Finerenone	Spironolactone	Spironolactone and HCTZ
Edematous Conditions				
Maintenance therapy together with bed rest and the restriction of fluid and sodium in patients with cirrhosis of the liver accompanied by edema and/or ascites			✔	✔
Management of edema and sodium retention when the patient is only partially responsive to, or is intolerant of, other therapeutic measures			✔	✔
Nephrotic patients when treatment of the underlying disease, restriction of fluid and sodium intake, and the use of other diuretics do not provide an adequate response			✔	✔
Patients with congestive heart failure taking digitalis when other therapies are considered inappropriate			✔	✔
Heart Failure				
Increase survival and reduce the need for hospitalization for heart failure when used in addition to standard therapy in patients with severe heart failure (New York Heart Association functional class III-IV)			✔	
Hypertension				
Essential hypertension				✔ *
Hypertension	✔ †		✔ ‡	
Hypokalemia				
Prophylaxis of hypokalemia in patients taking digitalis when other measures are considered inadequate or inappropriate			✔	

Indication(s)	Single Entity Agents			Combination Products
	Eplerenone	Finerenone	Spironolactone	Spironolactone and HCTZ
Treatment of a diuretic-induced hypokalemia in patients with congestive heart failure when other measures are considered inappropriate				✔
Treatment of diuretic-induced hypokalemia in patients with hypertension when other measures are considered inappropriate				✔
Treatment of patients with hypokalemia when other measures are considered inappropriate or inadequate			✔	
Myocardial Infarction				
To improve survival of stable patients with left ventricular systolic dysfunction (ejection fraction ≤40%) and clinical evidence of congestive heart failure after an acute myocardial infarction	✔			
Primary Hyperaldosteronism				
Establish the diagnosis of primary hyperaldosteronism by therapeutic trial			✔	
Short-term preoperative treatment of patients with primary hyperaldosteronism			✔	
Long-term maintenance therapy for patients with discrete aldosterone-producing adrenal adenomas who are judged to be poor operative risks or who decline surgery			✔	
Long-term maintenance therapy for patients with bilateral micro or macronodular adrenal hyperplasia (idiopathic hyperaldosteronism)			✔	
Diabetic Kidney Disease				
To reduce the risk of sustained eGFR decline, end stage kidney disease, cardiovascular death, non-fatal myocardial infarction, and hospitalization for heart failure in adult patients with chronic kidney disease associated with type 2 diabetes		✔		

*In patients in whom other measures are considered inadequate or inappropriate.
†Alone or in combination with other antihypertensive agents.
‡Usually in combination with other drugs, in patients who cannot be treated adequately with other agents or for whom other agents are considered inappropriate.
eGFR=estimated glomerular filtration rate, HCTZ=hydrochlorothiazide

IV. Pharmacokinetics

The pharmacokinetic parameters of the mineralocorticoid (aldosterone) receptor antagonists are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Mineralocorticoid (Aldosterone) Receptor Antagonists[2]

Generic Name(s)	Bioavail-ability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					

Generic Name(s)	Bioavail-ability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Eplerenone	69	50	Liver, extensive (% not reported)	Renal (67) Feces (32)	3 to 6
Finerenone	44	92	Liver (% not reported)	Renal (80) Feces (20)	2 to 3
Spironolactone	73	90	Liver (% not reported) Renal (% not reported	Renal (47 to 57) Feces (35 to 41)	1.3 to 1.4
Combination Products					
Spironolactone and HCTZ	73/ 60 to 80	90/40	Liver (% not reported) Renal (% not reported	Feces (35 to 41) Renal (47 to 57)/ Renal (50 to 70)	1.3 to 1.4/ 4 to 5

HCTZ=hydrochlorothiazide

V. Drug Interactions

Major drug interactions with the mineralocorticoid (aldosterone) receptor antagonists are listed in Table 5.

Table 5. Major Drug Interactions with the Mineralocorticoid (Aldosterone) Receptor Antagonists[2]

Generic Name(s)	Interaction	Mechanism
Mineralocorticoid receptor antagonists (eplerenone, spironolactone)	ACE inhibitors	Serious hyperkalemia, possibly with cardiac arrhythmias or arrest, may occur with the combination of aldosterone blockers and ACE inhibitors. Potassium sparing effects are additive when combining ACE inhibitors with aldosterone blockers. Aldosterone acts in the renal cortical collecting ducts by inducing synthesis of proteins that constitute the Na+, K+-ATPase pump. The pump acts to reabsorb sodium and water in exchange for potassium, which is then eliminated in the urine. Aldosterone antagonism can cause hyperkalemia.
Mineralocorticoid receptor antagonists (eplerenone)	Amiloride	Aldosterone blockers and amiloride may exert additive pharmacologic effects. Hyperkalemia with the potential for cardiac arrhythmias may result. Aldosterone blockers and amiloride may cause additive adverse effects when co-administered.
Mineralocorticoid receptor antagonists (eplerenone, spironolactone)	Potassium Preparations	Potassium preparations will increase serum potassium concentrations. This may increase the potential for clinically important hyperkalemia, especially when used concomitantly with aldosterone blockers.
Mineralocorticoid receptor antagonists (eplerenone, spironolactone)	Triamterene	Eplerenone and triamterene may exert additive pharmacologic effects. Hyperkalemia with the potential for cardiac arrhythmias may result.
Mineralocorticoid receptor antagonists (eplerenone)	HIV Protease Inhibitors	Inhibition of CYP3A4 isoenzymes by HIV protease inhibitors may decrease the metabolic elimination of aldosterone blockers. HIV protease inhibitors may increase plasma concentrations and pharmacologic or toxic effects of aldosterone blockers.
Mineralocorticoid receptor antagonists (eplerenone)	Imidazoles	Certain azole antifungal agents may decrease the elimination of eplerenone by inhibiting its hepatic metabolism via CYP3A4 isoenzyme resulting in increased concentration and consequently increased pharmacologic and toxic (hyperkalemia associated with potentially fatal arrhythmias) effects of eplerenone.
Mineralocorticoid receptor antagonists	Macrolides	Macrolides may decrease the elimination of eplerenone by inhibiting its hepatic metabolism via CYP3A4 isoenzyme

Generic Name(s)	Interaction	Mechanism
(eplerenone)		resulting in increased concentration and consequently increased pharmacologic and toxic (hyperkalemia associated with potentially fatal arrhythmias) effects of eplerenone.
Mineralocorticoid receptor antagonists (eplerenone)	Nefazodone	Nefazodone may decrease the elimination of eplerenone by inhibiting its hepatic metabolism via CYP3A4 isoenzyme resulting in increased concentration and consequently increased pharmacologic and toxic (hyperkalemia associated with potentially fatal arrhythmias) effects of eplerenone. Coadministration of eplerenone with nefazodone is contraindicated.
Mineralocorticoid receptor antagonists (eplerenone)	Spironolactone	Eplerenone and spironolactone may exert additive pharmacologic effects. Hyperkalemia with the potential for cardiac arrhythmias may result.
Mineralocorticoid receptor antagonists (eplerenone)	Verapamil	Inhibition of CYP3A4 isoenzymes by verapamil may decrease the metabolic elimination of eplerenone. Verapamil may increase plasma concentrations and pharmacologic or toxic effects of eplerenone.
Mineralocorticoid receptor antagonists (spironolactone)	Angiotensin II Receptor Antagonists	Decreased aldosterone activity by angiotensin II receptor antagonists may function synergistically with potassium conservation by spironolactone to produce substantial hyperkalemia. The risk of hyperkalemia may be increased when spironolactone is co-administered with angiotensin II receptor antagonists.
Mineralocorticoid receptor antagonists (spironolactone)	Eplerenone	Concurrent use of eplerenone and spironolactone may result in increased risk of hyperkalemia.
Mineralocorticoid receptor antagonists (spironolactone)	Digoxin	Concurrent use of digoxin and spironolactone may result in increased digoxin exposure.
Thiazide diuretics (HCTZ)	Dofetilide	Thiazide diuretics may induce hypokalemia which may increase the risk of torsades de pointes. The coadministration of dofetilide with a thiazide diuretic is contraindicated.
Mineralocorticoid receptor antagonists (spironolactone)	Lithium	Concurrent use of lithium and spironolactone may result in increased lithium concentrations and lithium toxicity (weakness, tremor, excessive thirst, confusion).
Mineralocorticoid receptor antagonists (finerenone)	Strong CYP3A4 inhibitors	Concurrent use of finerenone and strong CYP3A4 inhibitors may result in increased finerenone exposure.
Mineralocorticoid receptor antagonists (finerenone)	Moderate or weak CYP3A4 inhibitors	Concurrent use of finerenone and moderate or weak CYP3A4 inhibitors may result in increased finerenone exposure.
Mineralocorticoid receptor antagonists (finerenone)	Strong or moderate CYP3A4 inducers	Concurrent use of finerenone and strong or moderate CYP3A4 inducers may result in decreased finerenone exposure.
Thiazide diuretics (HCTZ)	Diazoxide	The combination of diazoxide with a thiazide diuretic may lead to hyperglycemia though an unknown mechanism; therefore the combination should be avoided. When used together, blood and urine glucose levels should be frequently monitored, and dosage reductions may be required.
Thiazide diuretics (HCTZ)	Digitalis glycosides	Thiazide diuretics may induce electrolyte disturbances which may predispose patients to digitalis-induced arrhythmias. Measure plasma levels of potassium and magnesium, supplement low levels, and use dietary sodium restriction or potassium-sparing diuretics to prevent further losses.

ACE inhibitors=angiotensin converting enzyme inhibitors, CYP=cytochrome P450 isoenzyme, HCTZ=hydrochlorothiazide, HIV=human immunodeficiency virus

VI. Adverse Drug Events

The most common adverse drug events reported with the mineralocorticoid (aldosterone) receptor antagonists are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Mineralocorticoid (Aldosterone) Receptor Antagonists[1-7]

Adverse Events	Single Entity Agents			Combination Products
	Eplerenone	Finerenone	Spironolactone	Spironolactone and HCTZ
Cardiovascular				
Hypotension	-	4.8	-	-
Orthostatic hypotension	-	-	-	✔
Central Nervous System				
Ataxia	-	-	✔	✔
Confusion	-	-	✔	✔
Dizziness	3	-	-	✔
Drowsiness	-	-	✔	✔
Fatigue	2	-	✔	✔
Fever	-	-	✔	✔
Headache	-	-	✔	✔
Insomnia	-	-	-	✔
Lethargy	-	-	✔	✔
Restlessness	-	-	-	✔
Vertigo	-	-	-	✔
Dermatological				
Alopecia	-	-	-	✔
Cutaneous vasculitis	-	-	-	✔
Erythema multiforme	-	-	-	✔
Exfoliative dermatitis	-	-	-	✔
Maculopapular eruptions	-	-	-	✔
Necrotizing angiitis	-	-	-	✔
Photosensitivity	-	-	-	✔
Pruritus	-	-	-	✔
Purpura	-	-	-	✔
Rash	<1	-	✔	✔
Stevens-Johnson syndrome	-	-	-	✔
Toxic epidermal necrolysis	-	-	-	✔
Urticaria	-	-	✔	✔
Endocrine and Metabolic				
Amenorrhea	-	-	✔	✔
Breast cancer	-	-	✔	✔
Deepening of the voice	-	-	✔	✔
Dehydration	-	-	✔	✔
Gynecomastia	≤1	-	9	9
Hyperchloremic metabolic acidosis	-	-	✔	✔
Irregular menses	-	-	✔	✔
Mastodynia	≤1	-	2	2
Postmenopausal bleeding	-	-	✔	✔
Gastrointestinal				
Abdominal pain	1	-	-	✔
Anorexia	-	-	✔	✔

Adverse Events	Single Entity Agents			Combination Products
	Eplerenone	Finerenone	Spironolactone	Spironolactone and HCTZ
Cholestatic toxicity	-	-	✔	✔
Constipation	-	-	-	✔
Cramping	-	-	✔	✔
Diarrhea	2	-	✔	✔
Gastritic bleeding	-	-	✔	✔
Gastritis	-	-	✔	✔
Nausea	-	-	✔	✔
Pancreatitis	-	-	-	✔
Sialoadenitis	-	-	-	✔
Ulceration	-	-	✔	✔
Vomiting	-	-	✔	✔
Xerostomia	-	-	✔	✔
Genitourinary				
Abnormal vaginal bleeding	≤2	-	-	-
Albuminuria	1	-	-	-
Glucosuria	-	-	-	✔
Impotence	-	-	✔	✔
Interstitial nephritis	-	-	-	✔
Renal dysfunction	-	-	✔	✔
Renal failure	-	-	✔	✔
Hematologic				
Agranulocytosis	-	-	✔	✔
Aplastic anemia	-	-	-	✔
Eosinophilia	-	-	✔	✔
Hemolytic anemia	-	-	-	✔
Leukopenia	-	-	-	✔
Thrombocytopenia	-	-	-	✔
Laboratory Test Abnormalities				
Blood urea nitrogen increased	<1	-	✔	✔
Creatinine increased	6	-	-	-
Hypercholesterolemia	≤1	-	-	-
Hyperglycemia	-	-	-	✔
Hyperkalemia	≤32	18.3	≤40	≤40
Hypertriglyceridemia	<15	-	-	-
Hyponatremia	2	1.4	✔	✔
Hyperuricemia	<1	-	-	✔
Liver function tests increased	<1	-	-	-
Respiratory				
Cough	2	-	-	-
Respiratory distress	-	-	-	✔
Other				
Anaphylaxis	-	-	✔	✔
Angioneurotic edema	<1	-	-	-
Blurred vision	-	-	-	✔
Flu-like syndrome	2	-	-	-
Hepatocellular toxicity	-	-	✔	✔
Jaundice	-	-	-	✔
Muscle cramps	-	-	-	✔
Vasculitis	-	-	✔	✔
Weakness	-	-	-	✔
Xanthopsia	-	-	-	✔

✓ Percent not specified
-Event not reported

VII. Dosing and Administration

The usual dosing regimens for the mineralocorticoid (aldosterone) receptor antagonists are listed in Table 7.

Table 7. Usual Dosing Regimens for the Mineralocorticoid (Aldosterone) Receptor Antagonists[1-7]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Eplerenone	Heart Failure: Tablet: initial, 25 mg once daily for four weeks; maintenance, 50 mg once daily Hypertension: Tablet: initial, 50 mg once daily; maximum, 50 mg twice daily	Safety and efficacy in children have not been established.	Tablet: 25 mg 50 mg
Finerenone	Chronic kidney disease associated with type 2 diabetes: Tablet: initial, 10 to 20 mg once daily based on estimated glomerular filtration rate; target dose is 20 mg once daily	Safety and efficacy in children have not been established.	Tablet: 10 mg 20 mg
Spironolactone	Edema (congestive heart failure, hepatic cirrhosis, nephrotic syndrome): Tablet: initial, 100 mg once daily in a single or divided dose(s); maintenance, 25 to 200 mg once daily Edema caused by cirrhosis: Suspension: initiate therapy in a hospital setting and titrate slowly; initial, 75 mg (15 mL) per day in single or divided doses; in patients requiring titration above 100 mg, use another formulation Heart failure (Severe NYHA function class III to IV) Suspension: initial, 20 mg (4 mL) once daily; maintenance, 37.5 mg (7.5 mL) once daily Tablet: initial, 25 mg once daily; maintenance, 25 mg every other day to 50 mg once daily Hypertension Suspension: 20 mg (4 mL) to 75 mg (15 mL) per day in single or divided doses Tablet: initial, 50 to 100 mg once daily in a single or divided dose(s); maintenance, 25 to 200 mg once daily; maximum, 400 mg/day Hypokalemia: Tablet: 25 to 100 mg once daily Primary hyperaldosteronism (diagnosis): Tablet (long test): 400 mg/day for three to four weeks Tablet (short test): 400 mg daily for four days	Safety and efficacy in children have not been established.	Suspension: 25 mg/5 mL Tablet: 25 mg 50 mg 100 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Primary hyperaldosteronism (short-term preoperative therapy): Tablet: 100 to 400 mg/day prior to surgery Primary hyperaldosteronism (long-term maintenance therapy): Tablet: initial, 100 to 400 mg/day; maximum, 400 mg/day		
Combination Products			
Spironolactone and HCTZ	Edema (congestive heart failure, hepatic cirrhosis, nephrotic syndrome): Tablet: maintenance, 100-100 mg/day in a single or divided dose(s); maintenance, 25-25 to 200-200 mg/day Hypertension: Tablet: maintenance, 50-50 to 100-100 mg/day in a single or divided dose(s)	Safety and efficacy in children have not been established.	Tablet: 25-25 mg 50-50 mg

HCTZ=hydrochlorothiazide

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the mineralocorticoid (aldosterone) receptor antagonists are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Mineralocorticoid (Aldosterone) Receptor Antagonists

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Diabetes/Diabetic Nephropathy/Renal Disease				
Bianchi et al.[31] (2006) Spironolactone 25 mg/day vs placebo All patients were receiving conventional therapy (ACE inhibitor and/or ARB).	OL, PC, PRO, RCT Adult patients with chronic kidney disease	N=165 1 year	Primary: Change in proteinuria, eGFR, blood pressure, and serum potassium Secondary: Not reported	Primary: While there was a significant reduction in proteinuria from baseline among spironolactone-treated patients (P<0.001), there was no difference in placebo-treated patients (P>0.05). At one year, there was no significant difference between spironolactone- and placebo-treated patients in eGFR (P value not reported). However, spironolactone-treated patients exhibited a lower monthly rate of decrease in eGFR from baseline compared to conventional therapy-treated patients (P<0.01). Patients whose baseline eGFR was <60 mL/min experienced a greater decline in eGFR compared to patients with baseline eGFR >60 mL/min (P<0.01). At one year of therapy, spironolactone-treated patients experienced a reduction in blood pressure from baseline (P<0.05). In contrast, placebo-treated patients did not exhibit blood pressure reduction from baseline (P value not reported). While there was a significant increase in serum potassium from baseline among spironolactone-treated patients (P<0.001), there was no difference in placebo-treated (P>0.05). Secondary: Not reported
Bianchi et al.[32] (2010) Spironolactone 25 mg, ramipril 10 mg, irbesartan 300 mg, and atorvastatin 10	RCT, OL Patients with a clinical diagnosis of idiopathic chronic glomerulonephritis and urine	N=128 36 months	Primary: Changes over time in proteinuria and eGFR Secondary: Adverse events,	Primary: SBP decreased more in the intensive-therapy group (from 156.6 to 113.5 mm Hg) than in the conventional therapy group (from 155.7 to 122.7 mm Hg; P<0.01). Urine protein excretion decreased from 2.65 to 0.45 g/g creatinine with intensive therapy (P<0.001). With conventional therapy, urine protein

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg QD (intensive therapy) vs ramipril 10 mg and atorvastatin 10 mg QD (conventional therapy) The addition of diuretics, calcium antagonists, β-blockers or α1-receptor antagonists were added to achieve blood pressure <130/80 mm Hg	protein-creatinine ratio >1 g/g		drop outs	excretion decreased from 2.60 to 1.23 g/g creatinine (P<0.001). With intensive therapy, eGFR did not significantly change over time (64.6 vs 62.9 mL/min/1.73 m^2). With conventional therapy, eGFR decreased from 62.5 to 55.8 mL/min/1.73 m^2 (P<0.01). Secondary: In the conventional therapy group, eight patients discontinued the study due to hyperkalemia, cough, and rapid deterioration in kidney function. In the intensive therapy group, 15 dropped out due to hyperkalemia, cough, and hypotension. Nine patients in the intensive therapy group developed gynecomastia. Twelve patients on conventional and 31 on intensive therapy had to interrupt the study temporarily because of low blood pressure. No patient developed an increase in creatine kinase, alanine aminotransferase, and alkaline phosphatase levels during the study.
Ogawa et al.[33] (2006) Spironolactone 25 mg/day plus imidapril* 5 mg/day vs furosemide 20 mg/day plus imidapril* 5 mg/day All patients were pre-treated with imidapril* for 1 year prior to trial onset.	PRO, RCT Adult patients with HTN and type 2 diabetes, with a urine albumin/ creatinine ratio >30 mg/g creatinine, and plasma BNP levels >100 pg/mL (suggestive of mild heart failure)	N=30 24 months	Primary: Change in BNP, urine albumin/ creatinine ratio and blood pressure Secondary: Not reported	Primary: At 12 months, spironolactone-treated patients exhibited a significant reduction in BNP level from baseline compared to furosemide-treated patients (P<0.05). At 12 months, spironolactone-treated patients exhibited a significant reduction in urine albumin/creatinine ratio from baseline compared to furosemide-treated patients (P<0.05). Both treatments exhibited similar reductions in blood pressure from baseline (P value not reported). No adverse events were reported in this trial. Secondary: Not reported
Chrysostomou et	DB, PC, RCT	N=41	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
al.[34] (2006) Spironolactone 25 mg/day plus irbesartan 150 mg/day and ramipril 5 mg/day vs ramipril 5 mg/day plus spironolactone 25 mg/day and placebo vs ramipril 5 mg/day plus irbesartan 150 mg/day and placebo vs ramipril 5 mg/day plus placebo and placebo	Patients 18 to 75 years of age, with a 24 hour urinary protein excretion >1.5 g/24 hours on ≥2 occasions ≥3 months apart, serum creatinine level ≤200 µmol/L with <20% variability in the preceding 3 months and treatment with an ACE inhibitor ≥6 months	6 months	Change in 24 hour urinary protein excretion at three months Secondary: Change in 24 hour urinary protein excretion at six months, change in blood pressure and creatinine clearance, adverse effects	Compared to ramipril-treated patients, the 24 hour urinary protein excretion reduction at three months was significantly greater in ramipril plus spironolactone-treated patients (P=0.004). Ramipril-, irbesartan- and spironolactone-treated patients exhibited a significant reduction in 24 hour urinary protein excretion compared to ramipril-treated patients (P<0.001). There was no significant difference in 24 hour urinary protein excretion with ramipril- and ramipril plus irbesartan-treated patients (P=1.00). At three months, spironolactone-treated patients exhibited a significant reduction in proteinuria from baseline (P≤0.001). In contrast, non-spironolactone-treated patients did not experience a significant reduction in proteinuria from baseline (P=0.840). Secondary: At six months, spironolactone-treated patients exhibited the greatest reduction in proteinuria compared to the other treatments (P<0.05). At six months, DBP was higher among ramipril monotherapy-treated patients compared to the other treatments (P=0.046). There was no difference in SBP among the treatments (P value not reported). There were no differences in creatinine clearance among the treatments (P>0.05). Gynecomastia was not observed with any of the treatments.
Furumatsu et al.[35] (2008) Spironolactone 25 mg/day (triple blockade group) vs	MC, OL, PRO, RCT Patients 20 to 70 years of age, with controlled blood pressure <130/80 mm Hg, chronic nephropathy (defined by serum	N=32 12 months	Primary: Reduction in proteinuria, urinary type IV collagen, SBP, DBP, mean blood pressure, creatinine, creatinine clearance,	Primary: At one year of therapy, patients randomized to the triple blockage group experienced a statistically significant 58% reduction in urinary protein level from baseline (P<0.05), while there was no difference in the control group. Compared to the control group, the triple blockade group experienced a significant reduction in proteinuria at one year of therapy (P<0.05). At one year of therapy, patients randomized to the triple blockage group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
trichlormethiazide* 1 mg/day or furosemide 10 mg/day (control group) Study medications were added to ongoing therapy consisting of enalapril 5 mg/day and losartan 50 mg/day.	creatinine level <3 mg/dL or calculated creatinine concentration <30 mL/min), daily treatment with enalapril 5 mg and losartan 50 mg for at least 12 weeks, and persistent proteinuria (urinary protein excretion >0.5 g/day)		potassium, urinary aldosterone Secondary: Not reported	experienced a statistically significant 40% reduction in urinary type IV collagen from baseline (P<0.05); while there was no difference in the control group. However there was no statistically significant difference in the change of urinary type IV collagen from baseline between the two study groups. There were no statistically significant differences between the two study groups in the following outcome measures: SBP, DBP, mean blood pressure, creatinine, creatinine clearance, potassium, and urinary aldosterone. Secondary: Not reported
van den Meiracker et al.[36] (2006) Spironolactone 25 mg BID vs placebo All patients were also receiving their ongoing antihypertensive therapy.	DB, PC, PG, RCT Adult patients with type 2 diabetes, macroalbuminuria (24 hour urinary albumin excretion >300 mg or urinary albumin to creatinine ratio >20 mg/mmol) despite use of an ACE inhibitor or ARB in recommended dosages for ≥1 year	N=59 1 year	Primary: Change in albuminuria, DBP and SBP, GFR, aldosterone level, plasma renin activity and serum potassium Secondary: Not reported	Primary: Compared to placebo-treated patients, spironolactone-treated patients exhibited a significant 40.6% reduction in albuminuria from baseline (P=0.002). Compared to placebo, spironolactone-treated patients exhibited a significant reduction in SBP from baseline (P=0.04), with a comparable reduction in DBP (P value not reported). Both treatments exhibited comparable changes in GFR from baseline (P value not reported). Compared to placebo, spironolactone-treated patients exhibited a significant increase in aldosterone level and plasma renin activity from baseline (P<0.05). There was a significant increase in serum potassium level in spironolactone-treated patients compared to placebo (P=0.02). Secondary: Not reported
Schjoedt et al.[37] (2006)	DB, RCT, XO Patients with	N=20 2 weeks	Primary: Change in proteinuria,	Primary: Compared to placebo, spironolactone therapy was associated with a significant 32% reduction in proteinuria from baseline (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Spironolactone 25 mg/day vs placebo Study medications were added to ongoing antihypertensive therapy (ACE inhibitor or ARB).	diabetic nephropathy and nephrotic range albuminuria (>2,500 mg/24 hour) despite recommended antihypertensive treatment		ambulatory DBP and SBP, GFR, fractional albumin clearance, aldosterone level, plasma renin activity, and serum potassium Secondary: Not reported	Compared to placebo, spironolactone therapy was associated with a significant reduction in systolic and diastolic ambulatory 24-hr blood pressures from baseline (P=0.004, P=0.001, respectively). Both groups exhibited comparable changes in GFR from baseline (P=0.13). Compared to placebo, spironolactone therapy was associated with a significant 31% reduction in fractional albumin clearance from baseline (P<0.001). Compared to placebo, spironolactone therapy was associated with significant increases in aldosterone level and plasma renin activity from baseline, 80 and 91%, respectively (P<0.005). There was a trend towards an increase in the serum potassium level with spironolactone therapy compared to placebo (P=0.054). Secondary: Not reported
Davidson et al.[38] (2008) Spironolactone 25 mg added to existing ACE inhibitor therapy	OL Patients ≥18 years of age with type 2 diabetes on an ACE inhibitor for >1 month with a urinary albumin to creatinine ratio >100 mg/g	N=24 12 weeks	Primary: Change in urinary albumin excretion Secondary: Changes in serum creatinine, serum potassium, and SBP	Primary: Urinary albumin excretion decreased 25.7% from a 404.6 mg/day to 302.7 mg/day (P<0.001). Urinary albumin excretion decreased 27.2% in the microalbuminuria group (P=0.05) and 24.3% in the macroalbuminuria group (P=0.02). Secondary: There were no significant changes in serum sodium, potassium, creatinine, or glucose. There was a significant decrease in SBP with the addition of spironolactone (141.2 to 132.5 mm Hg; P=0.002).
Saklayen et al.[39] (2008) Spironolactone 25	DB, PC, RCT, XO Patients with diabetic nephropathy	N=30 7 months	Primary: Blood pressure, serum creatinine, and spot urine	Primary: With spironolactone, the mean SBP at the beginning of the treatment period was 153.64 mm Hg and 141.60 at the end (P=0.01). DBP was 79.56 mm Hg at baseline and 76.68 at study endpoint (P=0.25). The mean SBP

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
to 50 mg/day vs placebo Study medications were added to existing ACE inhibitor or ARB therapy.	with any level of proteinuria who were already being treated with ACE inhibitor (lisinopril) or ARB (losartan) at moderate to maximum dose		protein/creatinine Secondary: Not reported	with placebo was 154.52 mm Hg at the beginning of the treatment period and 148.82 mm Hg at the end of the study period (P=0.34). DBP was 79.74 mm Hg at baseline and 77.91 at study endpoint (P=0.49). The urine protein/creatinine increased from 1.24 to 1.57 (24%) with placebo (P=0.35) and decreased from 1.80 to 0.79 (57%) with spironolactone (P=0.004). Serum creatinine increased from 1.43 to 1.50 on placebo (P=0.19) and from 1.35 to 1.56 on spironolactone (P=0.006). Secondary: Not reported
Sengul et al.[40] (2009) Spironolactone 25 mg QD Study medication was added to existing ACE inhibitor or ARB therapy.	PRO Patients with overt proteinuria (>300 mg/day) despite the regular use of ACE inhibitors and/or ARBs for ≥6 months	N=33 8 weeks	Primary: Proteinuria, blood pressure Secondary: Not reported	Primary: At week four, there was a 25.4% reduction in proteinuria with spironolactone (P=0.003). SBP and DBP were significantly reduced (P=0.013 and P=0.040, respectively). Serum potassium level increased 0.28 mEq/L (P<0.001). At week eight, the 24-hr median urinary protein excretion decreased from 1,428 to 743 mg/day (47.9%) with spironolactone. SBP and DBP were significantly reduced (P<0.004 and P<0.001, respectively). Serum potassium level increased 0.55 mEq/L (P<0.001). There was no difference in creatinine clearance or serum creatinine levels. Serum albumin increased from 3.88 to 4.01 g/dL (P=0.003). Secondary: Not reported
Tylicki et al.[41] (2008) Spironolactone 25 mg QD plus background therapy for 8 weeks (triple RAAS blockade)	OL, RCT, XO Patients with chronic nondiabetic proteinuric kidney diseases	N=18 16 weeks	Primary: 24-hr urine excretion of protein, blood pressure, serum creatinine, serum potassium, plasma renin activity	Primary: A total of 17 patients achieved blood pressure goal of <130/80 mm Hg. There was no difference in ambulatory SBP and DBP between the treatments (P=0.9 and P=0.1). Serum creatinine and eGFR remained stable during the study periods (P=0.6 and P=0.9, respectively). A significant increase in plasma renin activity was observed after

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs background therapy for 8 weeks (double RAAS blockade) Background therapy included HCTZ, telmisartan, cilazapril (ACE inhibitor).			Secondary: Not reported	treatment with triple RAAS blockade compared to double RAAS blockade (P=0.02). Triple RAAS therapy provided an additional 55.37% decrease in proteinuria compared to double RAAS blockade (P=0.01). The decrease in proteinuria was shown in 16 of 18 patients. Changes in proteinuria did not correlate with changes in SBP, DBP, or plasma renin activity. There was a significant increase in potassium levels after triple RAAS blockade compared to baseline (P=0.02). Secondary: Not reported
Heart Failure				
Pitt et al.[42] (2003) EPHESUS Eplerenone 25 mg/day for 4 weeks, followed by titration to 50 mg/day vs placebo Patients were allowed to receive optimal medical therapy (ACE inhibitors, ARBs, diuretics, β-blockers, coronary reperfusion therapy)	DB, MC, RCT Patients with acute MI, left ventricular dysfunction (ejection fraction ≤40%) and heart failure (patients with diabetes were not required to have heart failure)	N=6,632 16 months (mean follow-up)	Primary: Death from any cause, composite of death from cardiovascular causes or hospitalization for a cardiovascular event (heart failure, recurrent acute MI, stroke or ventricular arrhythmia) Secondary: Death from any cause or any hospitalization, death from cardiovascular causes, any hospitalization, hospitalization for	Primary: Significantly fewer eplerenone-treated patients died from any cause compared to placebo-treated patients (478 vs 554; RR, 0.85; 95% CI, 0.75 to 0.96; P=0.008). Significantly fewer eplerenone-treated patients died from or required hospitalization for cardiovascular events compared to placebo-treated patients (885 vs 993; RR, 0.87; 95% CI, 0.79 to 0.95; P=0.002). Secondary: Significantly fewer eplerenone-treated patients died from any cause or required hospitalization (1,730 vs 1,829; RR, 0.92; 95% CI, 0.86 to 0.98; P=0.02). Death from cardiovascular causes was 12.3 and 14.6% in eplerenone- and placebo-treated patients (RR, 0.83; 95% CI, 0.72 to 0.94; P=0.005). Fewer eplerenone-treated patients required hospitalization (1,493 vs 1,526; RR, 0.95; 95% CI, 0.89 to 1.02; P=0.2); however, the difference was not significant. Fewer eplerenone-treated patients required hospitalization due to a cardiovascular event (606 vs 649; RR, 0.91; 95% CI, 0.81 to 1.01;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			cardiovascular causes, hospitalization for heart failure, adverse events	P=0.09); however, the difference was not significant. There was a RR of 15% in the risk of hospitalization for heart failure in the eplerenone-treated patients (RR, 0.85; P=0.03) and 23% fewer episodes of hospitalization for heart failure were reported in these patients (RR, 0.77; P=0.002). Serious hyperkalemia (serum potassium ≥6.0 mmol/L) occurred in 5.5 and 3.9% of eplerenone- and placebo-treated patients (P=0.002). The incidence of hyperkalemia was higher among patients with a lower baseline creatinine clearance (P<0.001). At one year, the serum creatinine concentration had increased by 0.02 and 0.06 mg/dL in placebo- and eplerenone-treated patients (P<0.001). There were no significant differences between eplerenone- and placebo-treated patients in the incidence of sex hormone-related adverse events, including gynecomastia, impotence, breast pain and abnormal vaginal bleeding (P>0.05).
Pitt et al.[43] (2005) EPHESUS Eplerenone 25 mg/day for 4 weeks, followed by titration to 50 mg/day vs placebo Patients were allowed to receive optimal medical therapy (ACE	Subanalysis of EPHESUS Patients with acute MI, left ventricular dysfunction (ejection fraction ≤40%) and heart failure (patients with diabetes were not required to have heart failure)	N=6,632 30 days post random-ization	Primary: Death from any cause, composite of death from cardiovascular causes or hospitalization for a cardiovascular event at 30 days Secondary: Death from cardiovascular causes, sudden cardiac death, fatal or nonfatal heart failure hospitalization,	Primary: A significantly lower percentage of eplerenone-treated patients died from any cause (3.2 vs 4.6%; P=0.004). A lower percentage of eplerenone-treated patients died from or required hospitalization for cardiovascular events (8.6 vs 9.9%; P=0.074); however, the difference was not significant. Secondary: A significantly lower percentage of eplerenone-treated patients died from cardiovascular cause (3.0 vs 4.4%; P=0.003). A lower incidence of sudden cardiac death was noted among eplerenone-treated patients (0.9 vs 1.4%; P=0.051); however, the difference was not significant. A lower percentage of eplerenone-treated patients required hospitalization for fatal/nonfatal heart failure (3.4 vs 4.2%; P=0.106); however, the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
inhibitors, ARBs, diuretics, β-blockers, coronary reperfusion therapy)			adverse events	difference was not significant. There was no significant difference between the two treatments in the number of patients experiencing at least one adverse event during 30 days of therapy (P=0.29). At 30 days, the serum potassium concentration had increased by 0.17 and by 0.24 mmol/L in placebo- and eplerenone-treated patients (P<0.001).
Pitt et al.[44] (2006) EPHESUS Eplerenone 25 mg/day for 4 weeks, followed by titration to 50 mg/day vs placebo Patients were allowed to receive optimal medical therapy (ACE inhibitors, ARBs, diuretics, β-blockers, coronary reperfusion therapy)	Subanalysis of EPHESUS evaluating effects of eplerenone in patients with LVEF ≤30% Patients with acute MI, left ventricular dysfunction (ejection fraction ≤40%) and heart failure (patients with diabetes were not required to have heart failure)	N=2,106 16 months	Primary: Death from any cause, composite of death from cardiovascular causes or hospitalization for a cardiovascular event Secondary: Death from cardiovascular causes, sudden cardiac death, composite of heart failure death and heart failure hospitalizations	Primary: Eplerenone therapy was associated with a significant 21% reduction in the risk of all-cause mortality compared to placebo (P=0.012). Eplerenone therapy was associated with a significant reduction in the risk of the composite endpoint of death from cardiovascular causes or hospitalization for a cardiovascular event compared to placebo (P=0.001). Secondary: Eplerenone therapy was associated with a significant 23% reduction in the risk of cardiovascular mortality compared to placebo (P=0.008). The RR of sudden cardiac death was reduced by 33% (P=0.01) and the heart failure mortality/heart failure hospitalization composite endpoint was reduced by 25% (P=0.005) in eplerenone-treated patients compared to placebo-treated patients. At 30 days, eplerenone therapy was associated with RRRs of 43 (P=0.002), 29 (P=0.006) and 58% (P=0.008) for all-cause mortality, the cardiovascular mortality/cardiovascular hospitalization composite endpoint for sudden cardiac death.
O'Keefe et al.[45] (2007) EPHESUS Eplerenone 25 mg/day for 4 weeks, followed by	Subanalysis of EPHESUS evaluating effects of eplerenone in patients with diabetes	N=1,483 16 months	Primary: Death from any cause, composite of death from cardiovascular causes or hospitalization for	Primary: Eplerenone therapy was not associated with a significant reduction in the risk of all-cause mortality compared to placebo (P=0.131). Eplerenone therapy in diabetic patients was associated with a significant 17% reduction in the risk of death from cardiovascular causes or hospitalization for a cardiovascular event compared to placebo (P=0.031).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
titration to 50 mg/day vs placebo Patients were allowed to receive optimal medical therapy (ACE inhibitors, ARBs, diuretics, β-blockers, coronary reperfusion therapy)	Patients with acute MI, left ventricular dysfunction (ejection fraction ≤40%) and heart failure (patients with diabetes were not required to have heart failure)		a cardiovascular event Secondary: Death from cardiovascular causes, sudden cardiac death, hyperkalemia	Secondary: Eplerenone therapy was not associated with a significant reduction in the risk of cardiovascular mortality compared to placebo (P=0.128). Eplerenone therapy was not associated with a significant reduction in the risk of sudden cardiac death compared to placebo (P=0.533). Eplerenone therapy was associated with a greater incidence of hyperkalemia compared to placebo (5.6 vs 3.0%; P=0.015).
Gheorghiade et al.[46] (2009) EPHESUS Eplerenone 25 mg/day for 4 weeks, followed by titration to 50 mg/day vs placebo Patients were allowed to receive optimal medical therapy (ACE inhibitors, ARBs, diuretics, β-blockers, coronary reperfusion therapy)	Subanalysis of EPHESUS evaluating effects of eplerenone on length of stay and total days of heart failure hospitalization Patients with acute MI, left ventricular dysfunction (ejection fraction ≤40%) and heart failure (patients with diabetes were not required to have heart failure)	N=828 16 months	Primary: Mean length of stay/episode of heart failure hospitalization, total number of days of heart failure hospitalizations following the index hospitalization during the subsequent follow up period Secondary: Determine the difference between the five regions in the mean length of stay and the total number of days for	Primary: Over a mean follow up of 16 months, eplerenone therapy was associated with a significant reduction in the mean length of hospital stay/episode of heart failure hospitalization of 1.6 days (9.2 vs 10.8 days; P=0.019). Eplerenone-treated patients achieved a reduction in the total number of days of heart failure hospitalization/patient of 3.6 days (13.3 vs 16.9 days; P=0.0006). Secondary: The length of stay/heart failure hospitalization episode and total number of days of heart failure hospitalization/patient were consistently and similarly reduced in eplerenone-treated patients in all geographic regions as demonstrated by the nonsignificant interaction of study region on treatment effect (P=0.63 for length of stay/episode and P=0.45 for total hospitalization days for heart failure, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			heart failure hospitalization	
Adamopoulos et al.[47] (2010) EPHESUS Eplerenone 25 mg/day for 4 weeks, followed by titration to 50 mg/day vs placebo Patients were allowed to receive optimal medical therapy (ACE inhibitors, ARBs, diuretics, β-blockers, coronary reperfusion therapy)	Subanalysis of EPHESUS evaluating the differential effects of time-to-eplerenone initiation vs placebo Patients with acute MI, left ventricular dysfunction (ejection fraction ≤40%) and heart failure (patients with diabetes were not required to have heart failure)	N=6,632 16 months	Primary: Death from any cause, composite of death from cardiovascular causes or hospitalization for a cardiovascular event (heart failure, recurrent acute MI, stroke or ventricular arrhythmia) Secondary: Sudden cardiac death	Primary: "Earlier" eplerenone-treated patients had significantly lower event rates when compared to "earlier" placebo-treated patients for all-cause mortality (11.5 vs 16.1%) and the composite of cardiovascular hospitalization or death (24.0 vs 30.3%). No significant differences were found between "later" eplerenone- and placebo-treated patients. "Earlier" eplerenone therapy significantly reduced the risk for all-cause mortality (HR, 0.72; 95% CI, 0.58 to 0.89; P=0.002) and cardiovascular hospitalization or death (HR, 0.78; 95% CI, 0.67 to 0.90; P=0.001). Secondary: "Earlier" eplerenone-treated patients had significantly lower event rates when compared to "earlier" placebo-treated patients for sudden cardiac death (3.7 vs 6.9%). No significant differences were found between "later" eplerenone- and placebo-treated patients. "Earlier" eplerenone therapy significantly reduced the risk for sudden cardiac death (HR, 0.54; 95% CI, 0.38 to 0.77; P=0.001). In a head-to-head comparison between the two eplerenone treatment groups, "earlier" therapy was associated with significantly lower risk with respect to all endpoints. No significant difference was found in a direct comparison between the two placebo treatment groups.
Udelson et al.[48] (2010) Eplerenone 25 mg/day for 4 weeks, followed by 50 mg/day vs placebo	DB, MC, PC, PG, RCT Patients ≥21 years of age with current symptoms consistent of mild to moderate heart failure (NYHA Class II and III) who had LVEF ≤35% and were on therapy	N=226 36 weeks	Primary: Change in left ventricular end-diastolic volume index Secondary: Changes in left ventricular end-systolic volume index and LVEF,	Primary: Over 36 weeks, there was no evidence of an effect of eplerenone therapy on left ventricular end-diastolic volume index compared to placebo (P value not reported). Secondary: Over 36 weeks, there was no evidence of an effect of eplerenone therapy on left ventricular end-systolic volume index compared to placebo (P value not reported). Over 36 weeks, there was no evidence of an effect of eplerenone therapy

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	with an ACE inhibitor and/or ARB and β-blocker for ≥3 months and at a dose that has not been adjusted within the previous 4 weeks		markers of collagen turnover	on LVEF compared to placebo (P value not reported). During the course of treatment, eplerenone-treated patients exhibited a greater reduction in PINP and BNP compared to placebo-treated patients (P=0.01 and P=0.04, respectively). No difference between the two treatments was observed in the change from baseline to week 36 in PIIINP (P value not reported).
Zannad et al.[49] (2011) EMPHASIS-HF Eplerenone 25 mg QD for 4 weeks, followed by 50 mg QD vs placebo Randomization occurred within 6 months after hospitalization for a cardiovascular reason. Patients who had not been hospitalized for a cardiovascular reason within 6 months of the screening visit	DB, RCT Patients ≥55 years of age with NYHA Class II symptoms, and ejection fraction ≤30% and treatment with an ACE inhibitor, ARB or both and a β-blocker at the recommended dose or maximal tolerated dose	N=2,737 21 months (median follow up)	Primary: Composite of death from cardiovascular causes or a first hospitalization for heart failure Secondary: Hospitalization for heart failure or death from any cause, death from any cause, death from cardiovascular causes, hospitalization for any reason, hospitalization for heart failure	Primary: The primary composite endpoint occurred in 18.3 and 25.9% of eplerenone- and placebo-treated patients (HR, 0.63; 95% CI, 0.54 to 0.74; P<0.001). Secondary: Death from any cause or hospitalization for heart failure occurred in 19.8 and 27.4% of eplerenone- and placebo-treated patients (HR, 0.65; 95% CI, 0.55 to 0.76; P<0.001). A total of 12.5 and 15.5% of eplerenone- and placebo-treated patients died (HR, 0.76; 95% CI, 0.62 to 0.93; P=0.008). A total of 10.8 and 13.5% of deaths were attributed to cardiovascular causes in eplerenone- and placebo-treated patients (HR, 0.76; 95% CI, 0.61 to 0.94; P=0.01). A total of 29.9 and 35.8% of eplerenone- and placebo-treated patients were hospitalized for any reason (HR, 0.77; 95% CI, 0.67 to 0.88; P<0.001). Of the hospitalized patients, 12.0 vs 18.4% of eplerenone- and placebo-treated patients were hospitalized for heart failure (HR, 0.58; 95% CI, 0.47 to 0.70; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
could be enrolled if the plasma BNP was ≥250 pg/mL or if the plasma N-terminal pro-BNP was ≥500 pg/mL in men and ≥750 pg/mL in women.				
Eschalier et al.[50] (2013) EMPHASIS-HF Eplerenone 25 mg QD for 4 weeks, followed by 50 mg QD vs placebo	Subgroup analysis of EMPHASIS-HF Patients included in the EMPHASIS-HF trial aged ≥75 years with diabetes, CKD, and SBP <median (123 mm Hg)	N=2,737 21 months (median follow up)	Primary: Hospitalization for HF or death from cardiovascular causes Secondary: Serum potassium, hyperkalemia leading to study drug discontinuation, hospitalization for hyperkalemia and hospitalization for worsening renal function (WRF), change in eGFR	Primary: Eplerenone was effective at reducing the risk of cardiovascular death or HF hospitalization in the high-risk subgroups, which is consistent with result in the overall EMPHASIS-HF study population (HR, 0.63; 95% CI, 0.54 to 0.74; P<0.001). The HR for the primary outcome in the eplerenone group as compared with the placebo group was 0.66 (95% CI, 0.49 to 0.88; P=0.005) in patients ≥75 years of age, 0.54 (95% CI, 0.42 to 0.70; P<0.0001) in patients with diabetes, 0.62 (95% CI, 0.49 to 0.79; P=0.0001) in patients with CKD, and 0.63 (95% CI, 0.51 to 0.79; P<0.0001) in patients with SBP < median. Secondary: The number of patients with study drug stopped due to adverse events was evenly distributed within and among the study high-risk subgroups in patients age ≥75 years (18.2% in eplerenone vs 19.0% in placebo), in patients with SBP <123 mm Hg (16.6% in eplerenone vs 18.0% in placebo), in patients with CKD (16.1% in eplerenone vs 22.3% in placebo), and in patients with diabetes mellitus (15.1% in eplerenone vs 18.1% in placebo). In patients with CKD (eGFR <60 ml/min/1.73 m2), there were fewer patients in eplerenone group who had their treatment stopped due to an adverse event or due to any other reason than in placebo group.
Krum et al.[51] (2013) EMPHASIS-HF Eplerenone 25 mg QD for 4 weeks, followed by 50 mg	Subgroup analysis of EMPHASIS-HF Patients included in the EMPHASIS-HF trial analyzed according to the use	N=2,737 21 months (median follow up)	Primary: Hospitalization for HF or death from cardiovascular causes Secondary:	Primary: The beneficial clinical effects of eplerenone (as observed in the main study) were preserved for the EMPHASIS-HF primary end point in patients receiving higher doses of ACE Inhibitor or ARB, β-blocker, or both. P values for interaction between high and low doses for the EMPHASIS-HF primary end point were not significant.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD vs placebo	and dose of ACE inhibitors/ARBs, β-blockers, or both		Not reported	Secondary: Not reported
Girerd et al.[52] (2015) EMPHASIS-HF Eplerenone 25 mg QD for 4 weeks, followed by 50 mg QD vs placebo	Subgroup analysis of EMPHASIS-HF Patients included in the EMPHASIS-HF trial analyzed according to whether the treatment was initiated <42 or 42+ days after qualifying CV hospitalization	N=2,338 21 months (median follow up)	Primary: Composite of cardiovascular mortality or hospitalization for HF Secondary: Adverse effects	Primary: The relative rate reductions in CV death/hospitalization for HF, hospitalization for HF, and all-cause mortality were similar (P for interaction=0.65, 0.44, and 0.40, respectively) whether the treatment was initiated <42 or 42+ days after qualifying CV hospitalization. Absolute rate reductions were -5.61 (95% CI, -8.67 to -2.55) events per 100 patient-years in the <42 days group and -3.58 (CI, -6.37 to -0.79) in the 42+ days group. Regardless of the event considered, cumulative incidences of events in patients treated with eplerenone were lower than the rates observed in patients allocated to placebo in both the <42 and the 42+ days groups. Secondary: The adverse effects of eplerenone were also unaffected by the time from the qualifying CV hospitalization.
Pitt et al.[53] (1999) RALES Spironolactone 25 mg/day; in the absence of hyperkalemia, the dose could be increased to 50 mg/day after 8 weeks; if hyperkalemia developed the dose could be decreased to 25 mg every other day	DB, MC, RCT Patients with NYHA class 4 heart failure within 6 months and with NYHA class 3 to 4 at study onset, diagnosed with CHF ≥6 weeks, treated with an ACE inhibitor and a loop diuretic, with a LVEF ≤35%	N=1,663 24 months (mean follow-up)	Primary: Death from any cause Secondary: Death from cardiac causes, hospitalization for cardiac causes, combined incidence of death or hospitalization for cardiac causes, combined end point of death or hospitalizations from any cause,	Primary: There were 386 and 284 deaths from any cause in placebo- and spironolactone-treated patients (RR, 0.70; 95% CI, 0.60 to 0.82; P<0.001). Secondary: There were 314 and 226 deaths in placebo- and spironolactone-treated patients that were attributed to cardiac causes (RR, 0.69; 95% CI, 0.58 to 0.82; P<0.001). There were 753 and 515 hospitalizations for cardiac causes in placebo- and spironolactone-treated patients (RR, 0.70; 95% CI, 0.59 to 0.82; P<0.001). The combined end point of death from cardiac causes or hospitalizations from cardiac causes showed a 32% reduction in risk among spironolactone-treated patients compared to placebo-treated patients (RR, 0.68; 95% CI, 0.59 to 0.78; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo			combined end point of death from any cause or hospitalizations from cardiac causes, change in the NYHA class, adverse events	The combined end point of death or hospitalizations from any cause showed a 23% reduction in risk among spironolactone-treated patients compared to placebo-treated patients (RR, 0.77; 95% CI, 0.68 to 0.86; P<0.001). The combined end point of death from any cause or hospitalizations from cardiac causes showed a 32% reduction in risk among spironolactone-treated patients as compared to placebo-treated patients (RR, 0.68; 95% CI, 0.60 to 0.77; P<0.001). A significantly greater percentage of spironolactone-treated patients experienced improvement in the NYHA class compared to placebo-treated patients (41 vs 33%; P<0.001). Gynecomastia or breast pain was reported in 10 and 1% of spironolactone- and placebo-treated men (P<0.001). The incidence of hyperkalemia was minimal with both treatments.
Vardeny et al.[54] (2012) RALES Spironolactone 25 or 50 mg/day vs placebo	Post-hoc analysis Patients with NHYA class III or IV heart failure with an ejection fraction <35%	N=1,658 24 months (mean follow-up)	Primary: Death from any cause Secondary: Death from cardiac causes, hospitalization for cardiac causes, combined incidence of death or hospitalization for cardiac causes, combined end point of death or hospitalizations from any cause, combined end point of death from	Primary: Patients with reduced baseline eGFR exhibited similar RR reductions in all cause mortality and the composite of death or hospital stays for heart failure compared to patients with a baseline eGFR >60 mL/min/1.73 m2, and a greater absolute risk reduction compared to patients with a higher baseline eGFR (10.3 vs 6.4%). Worsening renal failure (17 vs 7%; P<0.001) was associated with an increased adjusted risk of death with placebo (HR, 1.9; 95% CI, 1.3 to 2.6) but not with spironolactone (HR, 1.1; 95% CI, 0.79 to 1.5; P=0.009). The risk of hyperkalemia and renal failure was higher in patients with worse baseline renal function and patients with worsening renal failure, particularly with spironolactone. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			any cause or hospitalizations from cardiac causes, change in the NYHA class, adverse events	
Vizzardi et al.[55] (2010) Spironolactone 25 mg QD, followed by up-titration every 2 weeks to 50 or 100 mg QD vs placebo	DB, PC, RCT Patients with clinical evidence of heart failure, NHYA class1 to 2 severity of symptoms at the time of enrollment and receiving optimal medical treatment maintained at stable doses for ≥6 months	N=158 6 months	Primary: Change in LVEF, left ventricular end-diastolic and -systolic volumes, left ventricular mass and laboratory examinations Secondary: Not reported	Primary: After six months, LVEF increased (P<0.001) and left ventricular end-diastolic and -systolic volumes decreased (P<0.001 for both) significantly in spironolactone-treated patients compared to placebo-treated patients. After six months, left ventricular mass decreased significantly in spironolactone-treated patients compared to placebo-treated patients (from 269±74 to 243±67 g vs 250±43 to 247±38 g; P<0.05). Serum potassium increased in spironolactone-treated patients from 4.2±0 to 4.6±0.3 mmol/L (P<0.001). Serum aldosterone and renin levels increased, respectively, from 157.1±1.03 to 205±56.5 pg/mL (P=0.08) and from 3.7±10.5 to 6.2±2.8 ng/mL/hr (P=0.03) in these patients. No significant changes were found in serum creatinine, serum urea nitrogen and uric acid. Secondary: Not reported
Chan et al.[56] (2007) Spironolactone 25 mg QD vs placebo All patients received candesartan 8	DB, PC, RCT Patients with LVEF <40% on ACE inhibitors for >6 months	N=48 1 year	Primary: Change in LVEF, left ventricular end-diastolic volume index, end-systolic volume index, left ventricular mass index, SBP, quality of life Secondary: Not reported	Primary: At one year, combination therapy was associated with a significant improvement in LVEF from baseline (P<0.01). At one year, combination therapy was associated with a significant reduction in left ventricular end-diastolic volume index from baseline (P<0.001). At one year, combination therapy was associated with a significant reduction in end-systolic volume index from baseline (P<0.0005). At one year, combination therapy was associated with a significant reduction in left ventricular mass index from baseline (P=0.002).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day.				At one year, combination therapy was associated with a significant reduction in SBP from baseline (P<0.05). The control group was not associated with significant improvements in any of the above primary outcome measures. The quality of life score improved in both study groups. Secondary: Not reported
Edelmann et al.[57] (2013) Aldo-DHF Spironolactone 25 mg QD vs placebo	DB, MC, PC, PRO, RCT Patients with chronic NYHA class II or III heart failure, preserved LVEF ≥50%, and evidence of diastolic dysfunction	N=422 12 months	Primary: Change in diastolic function and maximal exercise capacity Secondary: Left ventricular mass index, neuroendocrine activation, symptoms of heart failure, QOL, 6-minute walking distance	Primary: Diastolic function decreased from 12.7±3.6 to 12.1±3.7 with spironolactone and increased from 12.8±4.4 to 13.6±4.3 with placebo (adjusted mean difference, -1.5; 95% CI, -2.0 to -0.9; P<0.001). With regards to exercise capacity, peak VO2 did not significantly change with spironolactone vs placebo (from 16.3±3.6 to 16.8±4.6 vs from 16.4±3.5 to 16.9±4.4 mL/min/kg, respectively; adjusted mean difference, 0.1 mL/min/kg; 95% CI, -0.6 to 0.8; P=0.81). Secondary: Compared to placebo, treatment with spironolactone induced reverse modeling (left ventricular mass index declined; adjusted mean difference, -6 g/m^2; 95% CI, -10 to -1; P=0.009) and improved neuroendocrine activation (N-terminal pro-brain-type natriuretic peptide geometric mean ratio, 0.86; 95% CI, 0.75 to 0.99; P=0.03). Compared to placebo, spironolactone did not improve heart failure symptoms or QOL. Compared to placebo, spironolactone slightly reduced 6-minute walking distance (-15 m; 95% CI, -27 to -2; P=0.03).
Pitt et al.[58] (2014) TOPCAT	DB, MC, RCT Patients ≥50 years of age with at least 1	N=3445 3 years	Primary: Composite of death from cardiovascular	Primary: 18.6% of patients in the spironolactone group and 20.4% of patients in the placebo group had at least one confirmed primary-outcome event (P=0.14).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Spironolactone vs placebo	sign and 1 symptom of HF, a LVEF ≥45%, controlled BP, and potassium <5.0 mmol/L who were hospitalized in the previous year		causes, aborted cardiac arrest, or hospitalization for the management of heart failure Secondary: Death from any cause, hospitalization for any cause, hyperkalemia (K ≥5.5 mmol/L), hypokalemia (K <3.5 mmol/L), an elevated serum creatinine level (≥2 times the baseline value and above the upper limit of normal), and a serum creatinine level ≥3.0 mg/deciliter	Secondary: There were no significant differences between study groups in time to death from any cause or first hospitalization for any reason. Frequency of hospitalization for any reason (including recurrent hospitalization) did not differ significantly according to study group (36.8 hospitalizations per 100 person-years in the spironolactone group and 36.3 per 100 person-years in the placebo group; P=0.71). The spironolactone group had a higher rate of hyperkalemia (18.7 vs 9.1% in the placebo group) and a lower rate of hypokalemia (16.2 vs 22.9%). The spironolactone group was more likely to have a doubling of the serum creatinine level to a value above the upper limit of the normal range (10.2 vs 7.0%). However, there were no significant between-group differences in the proportion of patients with a serum creatinine level of 3.0 mg per deciliter or higher or who required dialysis.
Levy et al.[59] (1977) Spironolactone and HCTZ 25-25 mg/day (fixed-dose combination product) for 16 weeks following 8 weeks of furosemide monotherapy	DB, RCT Patients 27 to 79 years of age with arteriosclerotic heart disease, hypertensive heart disease, or rheumatic heart disease classes 1 to 3, and congestive heart failure requiring diuretic	N=32 24 weeks	Primary: Change in heart failure symptoms, glucose, renin concentration, calcium, blood urea nitrogen, uric acid, creatinine, aldosterone, serum potassium level, adverse effects Secondary:	Primary: The combination therapy group and furosemide monotherapy group exhibited comparable control of heart failure symptoms. The combination therapy group was associated with a significant decrease in glucose and an increase in plasma renin concentration compared to furosemide monotherapy group (P<0.01). There were no significant differences in calcium, blood urea nitrogen, uric acid, or creatinine between the study groups. There was a significant increase in aldosterone secretion among patients randomized to the spironolactone and HCTZ group compared to the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs furosemide 25 mg daily for 24 weeks	therapy		Not reported	furosemide group (P<0.01). There was no significant difference in serum potassium level between treatment groups. No serious adverse effects were observed in either of the study groups. Secondary: Not reported
Lee et al.[60] (2013) Patients receiving spironolactone vs patients not receiving spironolactone	OBS Patients with newly diagnosed HF with documented LVEF of <40% who had no aldosterone receptor antagonist use in the 12 months before study entry	N=2358 Median follow-up of 2.5 years	Primary: all-cause mortality, all-cause hospitalization, severe hyperkalemia, and acute kidney injury Secondary: Not reported	Primary: Incident spironolactone use was associated with lower crude rates of mortality (5.5 vs 9.8 per 100 person-years; P<0.01) and all-cause hospitalization (49.4 vs 56.1 per 100 person-years, P<0.05) compared with nonuse. After adjustment for differences in patient characteristics and concurrent use of other HF therapies, use of spironolactone was not significantly associated with either death (adjusted HR, 0.93; 95% CI, 0.60 to 1.44) or all-cause hospitalization (adjusted HR, 0.91; 95% CI, 0.77 to 1.08). Crude rates of acute kidney injury were also significantly lower during periods of spironolactone use (7.2 per 100 person-years) compared with periods of nonuse (16.2 per 100 person-years). Conversely, spironolactone use was associated with higher crude rates of severe hyperkalemia (4.8 per 100 person-years) compared with nonuse (1.6 per 100 person-years, P<0.001). After adjustment for potential confounders, incident spironolactone use was associated with a higher adjusted rate of severe hyperkalemia (adjusted HR, 3.46; 95% CI, 1.97 to 6.06) but not with acute kidney injury (adjusted HR, 0.66; 95% CI, 0.42 to 1.05). Secondary: Not reported
Inampudi et al.[61] (2014) Spironolactone on discharge	OBS hospitalized Medicare beneficiaries with HFrEF (EF <45%)	N=1140 1 year post-discharge	Primary: 30-day all-cause readmission Secondary: 30-day all-cause	Primary: Within 30 days postdischarge, unadjusted all-cause readmissions rates were 30% and 25% for patients receiving and not receiving spironolactone, respectively. Propensity score (PS)-adjusted HR (95% CI) associated with spironolactone use was 1.41 (1.04 to 1.90).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs No spironolactone on discharge	and advanced CKD		mortality, HF readmissions, and combined end point of all-cause mortality or all-cause readmission	Secondary: The risk of all-cause readmission (PS-adjusted HR, 1.36; 95% CI, 1.13 to 1.63) and the combined end point of all-cause readmission or all-cause mortality (PS-adjusted HR, 1.30; 95% CI, 1.09 to 1.54) during 1 year postdischarge were higher among patients in the spironolactone group.
Maisel et al.[62] (2014) COACH Spironolactone-treated patients vs patients not treated with spironolactone	Secondary analysis Patients enrolled in the COACH biomarker substudy	N=534 30 days	Primary: 30-day mortality and HF-related rehospitalization Secondary: Biomarker levels (NT-proBNP, ST2, Gal-3, and creatinine)	Primary: Spironolactone significantly reduced the 30-day composite of mortality and HF-related rehospitalization (HR, 0.538; 95% CI, 0.299 to 0.968; P=0.039). Secondary: Elevated NT-proBNP, creatinine, and ST2 were associated with increased 30-day mortality and HF-related hospitalizations. Spironolactone treatment was significantly beneficial in groups with elevations of Gal-3, ST-2, NT-proBNP, or creatinine (P=0.037, 0.007, 0.035, and 0.009, respectively). In contrast, spironolactone treatment effects were not significant for groups with lower levels of any biomarker.
Hyperaldosteronism				
Karagiannis et al.[63] (2008) Eplerenone 25 mg BID, titrated up to 200 mg/day if blood pressure remained ≥140/90 mm Hg vs spironolactone 25 mg BID, titrated up to 400 mg/day if blood pressure remained ≥140/90 mm Hg	OL, PRO, RCT Patients with bilateral hyper-aldosteronism	N=34 16 weeks	Primary: Percentage of patients whose blood pressure <140/90 mm Hg at week 16 Secondary: Adverse events	Primary: At 16 weeks, 76.5 and 82.4% of spironolactone- and eplerenone-treated patients, respectively, exhibited reductions in blood pressure to <140/90 mm Hg (P=1.00). Secondary: Serum potassium levels were normalized with both treatments after four weeks of therapy (P value not reported). Mild hyperkalemia was noted in two spironolactone 400 mg-treated patients and in three eplerenone 150 mg-treated patients. Two spironolactone-treated patients reported bilateral gynecomastia at week 16 (P value not reported). Switching from spironolactone 400 mg/day to eplerenone 150 mg/day was effective in resolving gynecomastia symptoms without disrupting blood pressure control.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
HCTZ 12.5 mg was added to the study regimen if blood pressure remained uncontrolled at week 16.				
Karashima et al.[64] (2015) Eplerenone 50 mg, titrated up to 100 mg/day if blood pressure remained ≥140/90 mm Hg vs spironolactone 25 mg, titrated up to 100 mg/day if blood pressure remained ≥140/90 mm Hg Calcium channel blocker was added to the study regimen if blood pressure remained uncontrolled at week eight.	OL Patients ≥18 years of age with HTN and primary aldosteronism	N=54 12 months	Primary: Blood pressure Secondary: Metabolic factors	Primary: Treatment with spironolactone or eplerenone significantly decreased systolic BP and diastolic BP from baseline (P<0.001). The BP-lowering effects between the two agents did not differ. Secondary: Urinary albumin excretion was significantly improved by treatment (P=0.024). Spironolactone significantly increased plasma aldosterone concentration compared with eplerenone (P=0.007). Plasma renin activity, serum potassium, eGFR and urinary albumin excretion did not differ between the two groups. The metabolic factors did not significantly differ between the two groups. Body weight, BMI, waist circumference, visceral and subcutaneous adipose tissue area were not different between the two groups. Although BMI and visceral adipose tissue area were significantly decreased in all patients (P<0.05), no significant differences in BMI, visceral adipose tissue and subcutaneous adipose tissue area were observed between the two groups. Two patients treated with spironolactone experienced gynecomastia. No patients treated with eplerenone showed gynecomastia.
Hypertension				
Kohvakka et al.[65] (1979) Amiloride 5 mg QD vs	PC, RCT, XO Patients 41 to 70 years of age with uncomplicated HTN, previously treated	N=31 3 months	Primary: Changes in blood pressure, serum potassium, sodium, creatinine, urate and total body	Primary: No significant changes in blood pressure were observed with any of the treatments (P values not reported). Mean serum potassium was reduced with all treatments except with spironolactone. KCl supplementation was least effective in elevating

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
triamterene 75 mg QD vs KCl 1,500 mg QD vs spironolactone 50 mg QD vs placebo All patients were also receiving HCTZ 50 mg QD.	with antihypertensive agents for 1 to 6 years		potassium Secondary: Not reported	serum potassium. Total body potassium remained constant throughout treatment (P values not reported). Serum sodium remained within normal limits with all treatments (P values not reported). There were no significant changes in mean serum creatinine with any of the treatments (P values not reported). Serum urate concentration increased significantly with all treatments, including HCTZ monotherapy (P values not reported). Secondary: Not reported
Dahlöf et al.[66] (1991) Hypertension (STOP) Atenolol 50 mg QD, HCTZ 25 mg QD plus amiloride 2.5 mg QD, metoprolol 100 mg QD, or pindolol 5 mg QD vs placebo	DB, MC, RCT Swedish men and women 70 to 84 years old with treated or untreated essential HTN defined as SBP ≥180 mm Hg with a DBP of ≥90 mm Hg, or DBP >105 mm Hg irrespective of the SBP measured on 3 separate occasions during a 1-month placebo run-in phase in previously	N=1,627 25 months	Primary: Frequency of stroke, MI, and other cardiovascular death Secondary: Not reported	Primary: The active treatments significantly reduced the number of all primary endpoints (94 vs 58; RR, 0.60; 95% CI, 0.43 to 0.85; P=0.0031), frequency of stroke (53 vs 29; RR, 0.53; 95% CI, 0.33 to 0.86; P=0.0081) and frequency of other cardiovascular deaths (13 vs 4; RR, 0.30; 95% CI, 0.07 to 0.97) compared to placebo. There was not a statistically significant decrease observed in the rate of MI between the active treatments and placebo (28 vs 25; RR, 0.87; 95% CI, 0.49 to 1.56). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	untreated patients			
White et al.[67] (2003) Eplerenone 25 mg QD vs eplerenone 50 mg QD vs eplerenone 100 mg QD vs eplerenone 200 mg BID vs placebo	DB, MC, RCT Adult patients with untreated HTN and seated SBP <180 mm Hg, DBP between 95 to 110 mm Hg, and the 24 hour mean DBP ≥85 mm Hg	N=400 12 weeks	Primary: Mean change from baseline in seated DBP at 12 weeks Secondary: Change from baseline in SBP, 24 hour SBP and DBP, heart rate, adverse events	Primary: Eplerenone 50, 100 and 200 mg-treated patients experienced significant mean reductions in DBP from baseline compared to placebo (P≤0.01). The reduction in BP in eplerenone 25 mg-treated patients failed to meet significance (P=0.10). Secondary: Eplerenone 50, 100 and 200 mg-treated patients experienced significant mean reductions in SBP from baseline compared to placebo (P≤0.01). All eplerenone-treated patients experienced significant reductions in 24 hour ambulatory blood pressure measurements compared to placebo (P<0.006 for SBP and P<0.005 for DBP). There were no significant differences from baseline in 24 hour mean heart rate with any eplerenone-treated patient compared to placebo (P value not reported). Treatment emergent adverse events were reported in 48 and 49% of eplerenone- and placebo-treated patients. None of the adverse events were significantly different between the treatments (P value not reported). Two cases of impotence, gynecomastia, menstrual abnormalities and female breast pain were reported during the trial; one case occurred in a placebo-treated patient and the other in an eplerenone 100 mg/day-treated patient.
Krum et al.[68] (2002) Eplerenone 50 to 100 mg/day vs placebo All patients were receiving	DB, MC, PG, RCT Patients 18 to 85 years of age taking an ACE inhibitor or an ARB for mild to moderate HTN (DBP ≥95 but <110 mm Hg and SBP <180 mm Hg), with potassium >3 mEq/L but ≤5 mEq/L	N=341 8 weeks	Primary: Mean change from baseline in trough cuff seated DBP and SBP at week eight Secondary: Percentage of responders (DBP <90 mm Hg or exhibited a ≥10	Primary: Eplerenone-treated patients exhibited a significant mean reduction from baseline in SBP compared to placebo-treated patients at eight weeks of therapy (P≤0.05), regardless of concurrent ACE inhibitor or ARB use. While eplerenone plus ARB-treated patients exhibited a significant mean reduction from baseline in DBP compared to ARB-treated patients at week eight (P≤0.05), eplerenone plus ACE inhibitor-treated patients experienced a reduction in baseline DBP similar to ACE inhibitor-treated patients (P value not reported). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
background ACE inhibitor or ARB monotherapy.			mm Hg reduction from baseline), adverse events	A significantly greater percentage of eplerenone plus ARB-treated patients exhibited a positive response to therapy compared to ARB-treated patients (P=0.003). No significant differences in response rate were observed between eplerenone plus ACE inhibitor- and ACE inhibitor-treated patients (P value not reported). Adverse effects were mild to moderate and were similar in eplerenone- and placebo-treated groups (P value not reported).
Weinberger et al.[69] (2002) Eplerenone 50 mg QD vs eplerenone 25 mg BID vs eplerenone 100 mg QD vs eplerenone 50 mg BID vs eplerenone 400 mg QD vs eplerenone 200 mg	DB, MC, PG, RCT Patients 21 to 80 years of age, with seated, cuff-assessed DBP ≥95 but <114 mm Hg, a 24 hour mean DBP >85 mm Hg	N=409 8 weeks	Primary: Mean change in seated DBP from baseline Secondary: Mean change from baseline in SBP, 24 hour SBP and DBP, renin, aldosterone levels	Primary: Eplerenone therapy, across all doses studied, was associated with a significant reduction from baseline in seated and standing DBP compared to placebo (P<0.05). The eplerenone 50 mg BID regimen was associated with a significant reduction in baseline seated and standing DBP compared to the eplerenone 100 mg QD regimen (P<0.05). However, there were no differences in DBP reduction between any of the other QD and BID eplerenone regimens (P value not reported). Compared to placebo, spironolactone therapy was associated with significant reductions in DBP (P≤0.001). The eplerenone 50 mg BID and 100 mg QD regimens were associated with DBP reductions comparable to 50 to 75% of the effect observed with the spironolactone 50 mg BID regimen (P value not reported). Secondary: Eplerenone therapy, across all doses studied, was associated with a significant reduction from baseline in seated and standing SBP compared to placebo therapy (P<0.05). The eplerenone 200 mg BID regimen was associated with a significant reduction in baseline seated and standing SBP compared to the eplerenone 400 mg QD regimen (P<0.05). However, there were no differences in SBP reduction between any of the other QD and BID eplerenone regimens (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BID vs spironolactone 50 mg BID vs placebo				Eplerenone therapy, across all doses studied, was associated with a significant reduction in ambulatory SBP and DBP compared to placebo therapy, as observed during a 24 hour monitoring (P<0.05). Compared to placebo, spironolactone was associated with a significant reduction in SBP (P≤0.001). The eplerenone 50 mg BID and 100 mg QD regimens were associated with SBP reductions comparable to 50 to 75% of the effect observed with the spironolactone 50 mg BID regimen (P value not reported). The incidence of adverse events in eplerenone-treated patients was similar to placebo-treated patients (P value not reported). Additionally, the incidence of adverse events was comparable with eplerenone- and spironolactone-treated patients (P value not reported). The spironolactone 50 mg BID regimen was associated with a significant increase from baseline in serum potassium level compared to the eplerenone 50 mg QD and 100 mg QD regimens, regardless of QD or BID dosing (P<0.05). Eplerenone therapy was not associated with an increased incidence of gynecomastia or impotence compared to placebo therapy. There were no treatment-related menstrual abnormalities reported with eplerenone therapy, while one spironolactone-treated patient reporting treatment related intermenstrual bleeding.
Hollenberg et al.[70] (2003) Eplerenone 50 mg/day vs amlodipine 2.5 mg/day	RCT Patients ≥50 years of age, with untreated SBP between 140 to 190 mm Hg	N=269 24 weeks	Primary: Change in SBP and DBP, discontinuation rate, symptom distress index, SF-36 Health Survey Secondary: Not reported	Primary: Both treatments exhibited similar reductions in SBP and DBP from baseline (P=0.01). The dropout rate was 50% greater in amlodipine-treated patients compared to eplerenone-treated patients (P value not reported). Symptom distress (technique used to assess the influence of drug treatment on quality of life) index was assessed and results favored eplerenone therapy (P=0.03).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Both medications were titrated to a maximum of 200 (eplerenone) or 10 (amlodipine) mg/day to achieve a SBP<140 mm Hg.				SF-36 Health Survey showed no significant difference between the two treatments (P value not reported). Both treatments experienced similar incidences of adverse effects (P value not reported). Eplerenone-treated patients did not experience breast pain/tenderness, breast enlargement, changes in menstruation, gynecomastia or loss of libido. Secondary: Not reported
White et al.[71] (2003) Eplerenone 50 mg/day vs amlodipine 2.5 mg/day Both medications were titrated to a maximum of 200 (eplerenone) or 10 (amlodipine) mg/day to achieve a SBP<140 mm Hg.	AC, DB, MC, RCT Patients ≥50 years of age with systolic HTN (seated clinic SBP 150 to 165 mm Hg with a pulse pressure ≥70 mm Hg or 165 to 200 mm Hg with a DBP ≤95 mm Hg)	N=269 24 weeks	Primary: Mean change from baseline in SBP, DBP, 24 hour ambulatory BP, pulse pressure, and heart rate at week 24; urine albumin/ creatinine ratio; adverse events Secondary: Not reported	Primary: Mean reduction in SBP from baseline was comparable in eplerenone- and amlodipine-treated patients (P=0.83). Eplerenone-treated patients exhibited significant reductions in DBP from baseline at 24 weeks of therapy compared to amlodipine-treated patients (P=0.014). The two treatments exhibited comparable decreases in 24 hour ambulatory BP, pulse pressure and heart rate after 24 weeks of therapy (P>0.05). Eplerenone-treated patients exhibited a significant reduction from baseline in the urine albumin/creatinine ratio compared to amlodipine-treated patients (P=0.002). Treatment-emergent adverse events were reported in 64 and 70% of eplerenone- and amlodipine-treated patients. The only adverse event that was significant between the two treatments was the incidence of edema (3.7 vs 25.5%; P<0.05). There were no reports of gynecomastia, breast tenderness or menstrual irregularities with either treatment. Secondary: Not reported
Williams et al.[72] (2004) Eplerenone 50 mg	AC, DB, MC, PG, RCT Patients ≥18 years of	N=499 12 months	Primary: Change in seated trough DBP at 6 months	Primary: At six months, both treatments exhibited comparable reductions in DBP from baseline (P=0.91).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD vs enalapril 10 mg QD Both medications were titrated to 200 (eplerenone) or 40 (enalapril) mg/day if needed for optimal blood pressure control (DBP < 90 mm Hg).	age with stage 1 to 2 HTN (seated DBP ≥90 but <110 mm Hg, with a seated SBP <190 mm Hg)		Secondary: Change in seated trough SBP at 6 months, reduction in SBP and DBP at 12 months, reduction in urine albumin/ creatinine ratio, adverse events	Secondary: At six months, both treatments exhibited comparable reductions in SBP from baseline (P=0.20). At 12 months, both treatments exhibited comparable reductions in SBP and DBP from baseline (P=0.25 and P=0.33). Eplerenone-treated patients exhibited a significant reduction from baseline in urine albumin/creatinine ratio compared to enalapril-treated patients (61.5 vs 25.7%; P=0.01). There were no significant differences in overall treatment-emergent adverse events between the two treatments (P value not reported). There were no sex hormone related adverse events in eplerenone-treated patients. There were no clinically significant differences between the two treatments in any of the laboratory tests assessed. There were two eplerenone- and enalapril-treated patients that experienced hyperkalemia of ≥5.5 mmol/L.
Flack et al.[73] (2003) Eplerenone 50 mg QD vs losartan 50 mg QD vs placebo Doses were increased if blood pressure remained uncontrolled.	DB, MC, PG, RCT Men and women ≥18 years old, with mild to moderate HTN, with SBP <180 mm Hg and DBP 95 to 109 mm Hg (off medication) or if patients were receiving antihypertensive therapy their blood pressure was <140/90 mm Hg	N=551 16 weeks	Primary: Mean change from baseline in DBP at 16 weeks Secondary: Mean change from baseline at 16 weeks in SBP, SBP and DBP within and between racial groups, response rate (defined as the percentage of patients with DBP <90 mm Hg or DBP ≥90 mm Hg but ≥10 mm Hg below baseline),	Primary: At 16 weeks, patients randomized to eplerenone exhibited significantly greater mean changes in DBP from baseline compared to either losartan- or placebo-treated groups (P<0.001). Secondary: At 16 weeks, patients randomized to eplerenone exhibited significantly greater mean changes in SBP from baseline compared to either losartan- or placebo-treated groups (P<0.001). At 16 weeks, African American patients randomized to eplerenone exhibited significantly greater mean changes in SBP and DBP from baseline compared to the placebo-treated African American patients (P<0.001). At 16 weeks, African American patients randomized to eplerenone exhibited significantly greater mean changes in SBP and DBP from baseline compared to the losartan-treated African American patients (P≤0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			urinary albumin/creatinine ratio, effect of eplerenone in patients with various baseline renin and aldosterone levels, adverse effects	At 16 weeks, white patients randomized to eplerenone exhibited significantly greater mean changes in SBP and DBP from baseline compared to the placebo-treated white patients (P=0.001). However, the difference in SBP- and DBP-lowering effects was not significant different between the eplerenone ad losartan groups (P=0.126, P=0.068, respectively). Significantly greater percentage of patients randomized to eplerenone exhibited a positive response to therapy compared to either placebo (64.5 vs 41.2%; P<0.001) or losartan group (64.5 vs 48.3%; P=0.003). The eplerenone group (regardless of race) exhibited statistically significant improvement in urinary albumin/creatinine ratio from baseline compared to placebo (P=0.003). However, the difference in urinary albumin/creatinine ratio change from baseline was not significantly different between the eplerenone and losartan groups (P=0.652). Compared to losartan, eplerenone was more effective in lowering SBP and DBP in patients with low-moderate baseline renin levels (P<0.05). However, the difference was not statistically significant in patients with high baseline renin levels. Compared to losartan, eplerenone was more effective in lowering SBP in patients with low or high baseline aldosterone levels (P<0.05). However, the difference was not statistically significant in patients with moderate baseline aldosterone levels. Compared to losartan, eplerenone was more effective in lowering DBP in patients with low baseline aldosterone levels (P<0.05). However, the difference was not statistically significant in patients with moderate-high baseline aldosterone levels. There were no significant differences in the incidence of adverse events noted in eplerenone, placebo or losartan groups. The reported incidence of gynecomastia, breast pain, menstrual abnormalities, impotence, hyperkalemia and decreased libido with eplerenone was low and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				comparable to losartan and placebo.
Hanazawa et al.[74] (abstract) (2011) Spironolactone 12.5 or 25 mg/day In addition to existing antihypertensive regimens (monotherapy with a calcium channel blocker, ACE inhibitor, or ARB).	PRO Patients with uncontrolled HTN	N=86 Not reported	Primary: Change in baseline blood pressure Secondary: Not reported	Primary: Morning home SBP/DBP reduction was similar among patients not controlled on a calcium channel blocker (n=30, -8.2/-2.6 mmHg), ACE inhibitor (n=22, -13.0/-4.7 mmHg), and ARB (n=34, -11.5/-5.1 mmHg). An increase in serum potassium correlated positively with the decline in morning SBP. Secondary: Not reported
Schersten et al.[75] (2002) Spironolactone 50 mg/day vs spironolactone 100 mg/day vs spironolactone 200 mg/day vs placebo	RCT, SB, XO Patients <75 years of age, with DBP 105 to 135 mm Hg, after 10 to 15 minutes of supine rest	N=45 11 months	Primary: Change from baseline in DBP and SBP, adverse effects Secondary: Not reported	Primary: All spironolactone-treated patients exhibited a significantly reduced BP level from baseline as compared to placebo (P<0.001). While spironolactone 200 mg/day-treated patients exhibited a significantly greater lowered mean supine SBP compared to spironolactone 50 mg/day-treated patients (P<0.05), the difference between spironolactone 50 mg- and 100 mg/day-treated patients was not significant (P value not reported). Spironolactone 200 mg/day-treated patients exhibited a significant reduction in mean upright SBP from baseline compared to spironolactone 100 mg/day- and 50 mg/day-treated patients (P<0.01). The difference in the lowering of DBP from baseline was not significantly different among any of the spironolactone-treated patients (P value not reported). Spironolactone 100 mg/day-treated patients exhibited a significant increase in baseline potassium and serum creatinine concentrations (P<0.05). However, spironolactone 50 mg/day-treated patients did not exhibit a change in potassium level from baseline (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Oxlund et al.[76] (2013) Spironolactone 25 mg (option to titrate to twice daily) vs placebo	DB, MC, RCT Patients aged 30 to 74 years with blood pressure at or above 130/80 mmHg despite triple antihypertensive therapy	N=119 16 weeks	Primary: Reduction of mean SBP and DBPs Secondary: Glycemic control, urinary albumin excretion, adverse effects	Primary: All measures of BP by office as well as ambulatory monitoring showed marginal, insignificant reductions in the placebo group and significant reductions in the spironolactone group. Maximum reduction of office BP (11.3/5.3 mmHg) was found at 8 weeks of treatment (P<0.0001), after which no further reduction was found. Mean daytime SBP/DBP at 16 weeks of follow-up was 137 (13)/75 (8) mmHg in the spironolactone group and 145 (12)/79 (7) mmHg in the placebo group, P=0.0001 for difference of systolic measures and P=0.0038 for diastolic. Secondary: Urinary albumin/creatinine ratio was reduced significantly in the spironolactone group (P=0.001), but not in the placebo group. There was a nonsignificant decrease of eGFR in the spironolactone group. Hb1Ac did not change during intervention. The frequency of adverse events was comparable in the two groups.
Václavík et al.[77] (2014) ASPIRANT-EXT Spironolactone 25 mg vs placebo	DB, MC, RCT Patients with office SBP >140 mm Hg or DBP >90 mm Hg despite treatment with at least 3 antihypertensive drugs, including a diuretic	N=150 8 weeks	Primary: Comparison of the fall of daytime systolic and diastolic pressure on ABPM between the spironolactone and placebo groups after 8 weeks of treatment Secondary: Nighttime BP, serum sodium, potassium, and creatinine, change in body weight	Primary: At 8 weeks, BP values were decreased more by spironolactone, with differences in mean fall of SBP of -9.8, -13.0, -10.5, and -9.9 mm Hg (P<0.001 for all) in daytime, nighttime, and 24-hour ambulatory BP monitoring and in the office. The respective DBP differences were -3.2, -6.4, -3.5, and -3.0 mm Hg (P=0.013, P<0.001, P=0.005, and P=0.003). Secondary: A small comparable weight gain was observed in both study groups. With spironolactone treatment, serum sodium decreased by a median of 1.0 mmol/L, and serum potassium increased by a median 0.4 mmol/L. The mean serum potassium increased during the 8 weeks of spironolactone treatment from 4.10 to 4.49 mmol/L, the highest reached serum potassium value at 8 weeks was 5.6 mmol/L.
Li et al.[78]	DB, MC, PC, RCT	N=304	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2010) Phase A Spironolactone 25 mg QD (low-dose), 25 mg BID (middle-dose), 50 mg BID (high-dose) for 6 weeks Phase B Spironolactone 25 mg QD, 25 mg BID, 50 mg BID for 4 weeks vs placebo	Children 4 to 16 years of age with SBP ≥95th percentile		Change in SBP during phase B Secondary: Change in DBP, safety	Change in SBP from baseline of phase B to the end of the study (differences from placebo) were -2.61, 2.32, and -2.76 mm Hg for the low-, middle-, and high-dose groups, respectively (P value not significant, P value not significant, P=0.048, respectively). Secondary: There were no significant effects of eplerenone on change in DBP from baseline of phase B to end of study compared to placebo. During phase A, adverse events were reported by 40.2% of subjects in the high-dose group, 30.6% of those in the middle-dose group, and 37.9% of those in the low-dose group. In phase B, there were no differences in adverse event frequencies between active therapy and placebo (high-dose: 38.4 vs 45.2%; middle-dose: 50.0 vs 25.0%; low-dose 26.9 vs 34.6%, eplerenone vs, placebo, respectively). Serious adverse events in phase A included diarrhea, sleep apnea, syncope, pericarditis, arthritis, pneumonia, sepsis, and pleural effusion. In phase B, serious adverse events included sleep apnea, abdominal pain, and fever.
Hood et al.[79] (2007) SALT Spironolactone 50 mg/day vs spironolactone 100 mg/day vs amiloride 20 mg/day vs	DB, RCT, XO Adult patients with seated blood pressure of 140/90 to 170/110 mm Hg, plasma renin of ≤12 mU/L, plasma aldosterone-renin ratio >750, previous fall in SBP ≥20 mm Hg after 1 month of OL treatment with spironolactone 50 mg/day	N=57 42 weeks	Primary: Change in blood pressure and plasma renin from baseline between spironolactone 100 mg/day and bendro-flumethiazide 5 mg/day Secondary: Change in blood pressure and plasma renin from baseline between amiloride and other diuretics and	Primary: Spironolactone 100 mg/day- and bendroflumethiazide 5 mg/day-treated patients did not exhibit a significant difference in BP reduction from baseline (P value not reported). Secondary: Spironolactone 50 mg/day-treated patients exhibited a significant decrease in blood pressure from baseline compared to bendroflumethiazide 2.5 mg/day-treated patients (P<0.01). Losartan 100 mg-treated patients exhibited a significant decrease in blood pressure from baseline compared to bendroflumethiazide 2.5 mg/day-treated patients (P<0.05). High-dose bendroflumethiazide- and amiloride-treated patients exhibited significantly greater reductions in blood pressure compared to the lower doses (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
amiloride 40 mg/day vs bendro-flumethiazide* 2.5 mg/day vs bendro-flumethiazide* 5 mg/day vs losartan 100 mg/day vs placebo			between lower and higher doses of each diuretic	Spironolactone-treated patients exhibited a four-fold increase in baseline renin level compared to a two-fold increase observed in bendroflumethiazide-treated patients (P=0.003).
Nash et al.[80] (1977) Spironolactone 50 mg BID vs spironolactone 100 mg BID vs	DB, RCT Male outpatients between the ages of 21 to 65 years, with essential HTN, DBP between 90 to 114 mm Hg	N=79 12 weeks	Primary: Change in SBP, DBP, blood urea nitrogen, serum potassium, gynecomastia Secondary: Not reported	Primary: At week 12, all study groups exhibited significant reductions in SBP and DBP from baseline (P<0.05). At week 12, all three spironolactone monotherapy groups exhibited statistically significant increases in blood urea nitrogen from baseline (P<0.05). At week 12, the HCTZ monotherapy group was associated with a statistically significant decrease in serum potassium levels (P<0.001). At week 12, all three spironolactone monotherapy groups exhibited statistically significant increases in serum potassium levels from baseline

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
spironolactone 200 mg BID vs HCTZ 50 mg BID vs spironolactone and HCTZ 25-25 mg BID (fixed-dose combination product)				(P<0.05). At week 12, the spironolactone and HCTZ combination group was not associated with statistically significant increases in serum potassium levels from baseline. A dose-related risk of gynecomastia was observed in the spironolactone-treated patients. Among patients treated with spironolactone 50, 100, or 200 mg BID; 5.5, 11.8, and 40% reported gynecomastia symptoms. Of the patients randomized to spironolactone and HCTZ combination product, 7.7% reported gynecomastia symptoms. Secondary: Not reported
Schrijver et al.[81] (1979) Spironolactone 50 mg BID for 8 weeks (single drug phase), with the addition of a placebo for subsequent 4 weeks (group IA) vs spironolactone 50 mg BID for 8 weeks (single drug phase), subsequently HCTZ 50 mg BID was added to the regimen for an additional 4 weeks	DB Patients, between 24 to 63 years of age, with DBP between 90 to 114 mm Hg	N=49 20 weeks (4-week placebo run-in, 8-week single drug therapy, 4-week two-drug therapy, 4-week recovery)	Primary: Change in MABP, serum potassium, uric acid level, blood glucose, blood urea nitrogen, creatinine, plasma renin activity, aldosterone, side effects Secondary: Not reported	Primary: Following eight weeks of therapy with a single drug, all study groups exhibited a statistically significant reduction in MABP from baseline (P<0.01). There were no significant differences in MABP reduction among the study groups. The addition of a second drug to the antihypertensive regimen was not associated with a significant improvement in MABP. At the end of the two-drug treatment period, there were no differences in MABP among any of the study groups. Spironolactone therapy was associated with a significant decrease in serum potassium concentration from baseline (P<0.001). Spironolactone regimens were not associated with a significant change in potassium levels from baseline. Following eight weeks of therapy with a single drug, HCTZ-treated patients experienced a statistically significant increase in uric acid from baseline (P<0.001). Groups IIA and IIB also experienced a significant but smaller increase in uric acid level from baseline (P<0.05) with no change in groups I and IV.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(group IB) vs spironolactone 100 mg BID for 8 weeks (single drug phase), with the addition of a placebo for subsequent 4 weeks (group IIA) vs spironolactone 100 mg BID for 8 weeks (single drug phase), subsequently HCTZ 50 mg BID was added to the regimen for an additional 4 weeks (group IIB) vs spironolactone 200 mg BID for 8 weeks (single drug phase), with the addition of a placebo for subsequent 4 weeks (group IIIA)				During the single-drug treatment phase, patients randomized to group I experienced a significant increase in blood glucose from baseline (P<0.05). During the single-drug treatment phase, all patients except those randomized to group I experienced a significant increase in blood urea nitrogen from baseline (P<0.05). During the single-drug treatment phase, patients randomized to groups I and II experienced a significant increase in serum creatinine from baseline (P<0.05). During the single-drug treatment phase, all treatment groups experienced a significant increase in plasma renin activity from baseline (P<0.01). The addition of HCTZ in the two-drug study phase was associated with a rise in plasma renin activity in all study groups (P<0.05). All treatment groups experienced a significant increase in plasma aldosterone from baseline (P<0.05). Gynecomastia was reported only by patients randomized to the higher-dose spironolactone groups. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs spironolactone 200 mg BID for 8 weeks (single drug phase), subsequently HCTZ 50 mg BID was added to the regimen for an additional 4 weeks (group IIIB) vs HCTZ 50 mg BID for 8 weeks (single drug phase), with the addition of a placebo for subsequent 4 weeks (group IVA) vs HCTZ 50 mg BID for 8 weeks (single drug phase), subsequently HCTZ 50 mg BID was added to the regimen for an additional 4 weeks (group IVB)				
Wray et al.[82] (2010)	DB, RCT Patients ≥60 years of	N=36 6 months	Primary: Blood pressure, sympathetic	Primary: Arterial blood pressure decreased significantly with spironolactone (SBP: 160 to 134 mm Hg and DBP: 77 to 68 mm Hg) and with HCTZ (SBP: 161

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Spironolactone 25 to 100 mg QD vs HCTZ 12.5 to 50 mg QD Patients also received potassium 0 to 40 mEq to maintain blinding.	age with stage 1 HTN		nervous system activity Secondary: Not reported	to 145 mm Hg and 78 to 73 mm Hg). There was no significant difference between the groups. Sympathetic nervous system activity was significantly reduced after spironolactone (plasma norepinephrine: 378 to 335 pg/mL; P=0.04; [3H]-norepinephrine release rate: 2.74 to 1.97 μg/min/m^2; P=0.04), but not with HCTZ (plasma norepinephrine: 368 to 349 pg/mL; P=0.47; [3H]-norepinephrine release rate: 2.63 to 2.11 μg/min/m^2; P=0.21). There were no instances of hyperkalemia, and no other adverse effects were reported. Secondary: Not reported
Krieger et al.[83] (2018) ReHOT Spironolactone 12.5 mg QD (could be titrated to 25 or 50 mg/ day) vs clonidine 0.1 mg BID (could be titrated to 0.2 or 0.3 mg BID)	OL, RCT Patients with resistant hypertension (no office and ambulatory BP monitoring control, despite treatment with 3 drugs, including a diuretic, for 12 weeks)	N=162 12 weeks	Primary: BP control (determined by office BP<140/90 and ambulatory 24-hour mean BP <130/80) Secondary: BP control by each evaluation method, absolute BP reduction	Primary: Compared with the spironolactone group, the clonidine group presented similar rates of achieving the primary end point (20.5 vs 20.8%, respectively; RR, 1.01; 95% CI, 0.55 to 1.88; P=1.00). Secondary: Secondary end point analysis showed similar office BP (33.3 vs 29.3%) and ambulatory BP monitoring (44 vs 46.2%) control for spironolactone and clonidine, respectively. However, spironolactone promoted greater decrease in 24-hour systolic and diastolic BP and diastolic daytime ambulatory BP than clonidine.
Bomback et al.[84] (2009) Spironolactone 12.5 mg QD for 4 weeks in addition to ACE inhibitor therapy	OL Patients with obesity, longstanding hypertension and evidence of target organ damage who	N=21 8 weeks	Primary: Change in 24-hour ambulatory blood pressure, changes in office blood pressure, nocturnal blood pressure, and	Primary: Mean office, 24-hr ambulatory, and nocturnal ambulatory blood pressures declined significantly during the four weeks of spironolactone therapy from 110.6 to 105.0 mm Hg (office P=0.004), 100.6 to 95.5 mm Hg (24-hr P=0.03) and 95.3 to 87.5 mm Hg (nocturnal P=0.004). The mean urine albumin: creatinine ratio dropped from 13.8 to 8.5 mg/g (P=0.002) during spironolactone therapy and returned to 13.2 mg/g after

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	were treated with ACE inhibitors		urine albumin: creatinine ratio Secondary: Not reported	the drug was withdrawn. Serum potassium was not significantly affected by spironolactone therapy. There was a significant increase in serum creatinine from 0.95 before therapy to 1.03 mg/dl after spironolactone. The eGFR decreased from 81.9 to 76.8 mL/min/1.73m^2. Secondary: Not reported
Williams et al.[85] (2015) PATHWAY-2 Twelve weeks of once daily treatment with each of spironolactone (25 to 50 mg), bisoprolol (5 to 10 mg), doxazosin modified release (4 to 8 mg), and placebo, in addition to their baseline blood pressure drugs	DB, PC, XO Patients 18 to 79 years of age with seated clinic SBP ≥ 140 mmHg (or ≥135 mmHg for patients with diabetes) and home SBP (18 readings over four days) ≥130 mmHg, despite treatment for at least three months with maximally tolerated doses of three drugs (an ACE or ARB, a CCB, and a diuretic)	N=335 12 months	Primary: Average home SBP, recorded in the morning and the evening in triplicate, on four consecutive days before study visits Secondary: Clinic SBP, BP control rates, adverse events	Primary: The average reduction in home SBP by spironolactone was significantly greater compared to placebo (–8.70 mmHg; 95% CI, −9.72 to −7.69; P<0.0001), to the mean of the other two active treatments (doxazosin and bisoprolol; −4.26; 95% CI, –5.13 to −3.38; P<0·0001), and to the individual treatments; versus doxazosin (–4.03; 95% CI, –5.04 to −3.02; P<0.0001) and versus bisoprolol (–4.48; 95% CI, –5.50 to −3.46; P<0.0001). Secondary: The results for seated clinic SBP largely mirror those seen with home SBP except that there was a large placebo effect on clinic BP that was not seen with home BP measurement. Overall 219 (68.9%; 95% CI, 63.6 to 73.8) of 314 patients achieved target home SBP of <135 mmHg. 58% of patients had their BP controlled with spironolactone, which was significantly greater than rates for other treatments (P<0.001 when compared to doxazosin, bisoprolol, and placebo). Most patients who were controlled by doxazosin or bisoprolol had a still greater fall in blood pressure on spironolactone, which was consequently the most effective treatment in almost 60% of patients. This was at least three times the proportion in whom doxazosin or bisoprolol were the most effective. All active treatments were well tolerated with similar low rates of adverse events and withdrawals due to adverse events.
Chapman et al.[86] (2007)	Subanalysis of ASCOT-BPLA	N=1,411	Primary: Change in DBP	Primary: Spironolactone-treated patients lead to a significant 21.9 mm Hg reduction

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ASCOT-BPLA Atenolol 50 to 100 mg titrated to target blood pressure <140/90 mm Hg (or <130/90 mm Hg in diabetic patients); bendro-flumethiazide* plus potassium 1.25 to 2.5 mg plus doxazosin were added for additional blood pressure control; if blood pressure remained elevated on the 3 above drugs, spironolactone 25 mg was added to the regimen vs amlodipine 5 to 10 mg titrated to target blood pressure <140/90 mm Hg (or <130/90 mm Hg in diabetic patients); perindopril 4 to 8 mg and doxazosin were added for additional control; if blood pressure remained elevated	evaluating effects of spironolactone on treatment-resistant HTN Patients 40 to 79 years of age with HTN and ≥3 cardiovascular risk factors, with SBP ≥160 mm Hg and/or DBP ≥100 mm Hg (not on antihypertensive therapy) or SBP ≥140 mm Hg and/or DBP ≥90 mm Hg (on antihypertensive therapy)	1.3 years	and SBP, adverse effects Secondary: Not reported	in SBP among patients whose blood pressure was previously uncontrolled on at least three other antihypertensive drugs (95% CI, 20.8 to 23.0 mm Hg; P<0.001). Spironolactone-treated patients lead to a significant 9.5 mm Hg reduction in DBP among patients whose blood pressure was previously uncontrolled on at least three other antihypertensive drugs (95% CI, 9.0 to 10.1; P<0.001). Spironolactone-treated patients exhibited small but significant decreases in sodium, LDL-C and TC as well as increases in potassium, glucose, creatinine and HDL-C (P<0.05). The most common adverse effect reported in the trial was gynecomastia in men (P value not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
on the 3 above drugs, spironolactone 25 mg was added to the regimen				
Diabetic Kidney Disease				
Filippatos et al.[87] (2021) FIDELIO-DKD Finerenone 10 or 20 mg QD vs placebo	DB, MC, PC, PG, RCT Patients ≥18 years of age with a clinical diagnosis of T2D and moderately elevated albuminuria and an eGFR ≥25 to <75mL/min/1.73m^2	N=5,674 Median follow-up 2.6 years (range, 2.0 to 3.4 years)	Primary: Composite cardiovascular outcome included time to first onset of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke or hospitalization for heart failure Secondary: Composite kidney outcome included time to first onset of kidney failure, a sustained ≥40% decrease in eGFR from baseline over at least four weeks, or renal death	Primary: Over a median follow-up of 2.6 years, finerenone reduced the risk of the composite cardiovascular outcome compared with placebo (HR, 0.86; 95% CI, 0.75 to 0.99; P=0.034), with no significant interaction between patients with and without CVD (HR, 0.85; 95% CI, 0.71 to 1.01 in patients with a history of CVD; HR, 0.86; 95% CI, 0.68 to 1.08 in patients without a history of CVD; P value for interaction=0.85). Secondary: The composite kidney outcome was lower with finerenone versus placebo; however, the effects were more pronounced in patients with a history of CVD than those without it (P value for interaction=0.016). In patients with a history of CVD, the composite kidney outcome occurred in 200 (15.3%) patients in the finerenone group and 267 (20.5%) patients in the placebo group (incidence rate per 100 patient-years, 6.6 and 9.06, respectively; HR, 0.70; 95% CI, 0.58 to 0.84). In patients without a history of CVD, the composite kidney outcome occurred in 304 (19.9%) patients in the finerenone group and 333 (21.6%) patients in the placebo group (incidence rate per 100 patient-years, 8.42 and 9.1, respectively; HR, 0.94; 95% CI, 0.81 to 1.10).
Pitt et al.[88] (2021) FIGARO-DKD Finerenone 10 mg or 20 mg QD vs	DB, MC, PC, RCT Patients ≥18 years of age with T2D and CKD treated with RAS inhibitor at the maximum dose on the manufacturer's	N=7,437 Median follow-up 3.4 year	Primary: Composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke or	Primary: The incidence of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure (the primary composite outcome) was significantly lower in the finerenone group than in the placebo group (458 of 3,686 patients [12.4%] vs. 519 of 3,666 patients [14.2%]; HR, 0.87; 95% CI, 0.76 to 0.98; P=0.03). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	label that di dnot cause unacceptable side effects		hospitalization for heart failure Secondary: Composite of the first occurrence of kidney failure, a sustained decrease from baseline of at least 40% in the eGFR for a period of at least four weeks or death from renal causes	There was no significant between-group difference in the incidence of the first secondary composite outcome of failure, a sustained decrease from baseline of at least 40% in the eGFR for a period of at least four weeks or death from renal causes (350 patients [9.5%] in the finerenone group and 395 [10.8%] in the placebo group; HR, 0.87; 95% CI, 0.76 to 1.01).
Miscellaneous				
Pitt et al.[89] (2003) 4E-Left Ventricular Hypertrophy Study Eplerenone 200 mg QD vs enalapril 40 mg QD vs enalapril 10 mg plus eplerenone 200 mg If the blood pressure was uncontrolled on study medication at	AC, DB, PGd, RCT Patients with left ventricular hypertrophy, a history of HTN and predominantly in sinus rhythm	N=153 9 months	Primary: Change in left ventricular mass as assessed by MRI Secondary: Reduction in SBP and DBP, response rate (DBP <90 mm Hg), change in urine albumin creatinine ratio	Primary: Both treatments were associated with a significant reduction in left ventricular mass from baseline (P<0.001). The difference in left ventricular mass reduction from baseline between the two treatments was not significant (P=0.258). While enalapril plus eplerenone therapy demonstrated a significantly greater reduction in left ventricular mass from baseline compared to eplerenone therapy (P=0.007); the effect was not statistically different from that observed with enalapril therapy (P=0.107). Secondary: The SBP was reduced significantly more in enalapril plus eplerenone-treated patients compared to eplerenone-treated patients (P=0.048). The other treatment groups exhibited statistically comparable reductions from baseline in mean SBP and DBP (P value not reported). While 70.0% of eplerenone-treated patients responded to therapy, 40.7% of enalapril-treated patients responded (P=0.003). In addition, 79.6% of enalapril plus eplerenone-treated patients responded to therapy compared to 40.7% enalapril-treated patients (P=0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
week 8, OL HCTZ 12.5 to 25 mg/day and/or amlodipine 10 mg/day were allowed.				Enalapril plus eplerenone therapy was associated with a significant reduction in urine albumin creatinine ratio compared to either eplerenone or enalapril therapy (P<0.05). Adverse events were reported with similar incidence among all treatment groups (P value not reported). Cough was significant in enalapril-treated patients compared to eplerenone-treated patients (P=0.033). Two cases of gynecomastia were reported (one eplerenone- and one enalapril plus eplerenone-treated patients). Four patients (three enalapril- and one enalapril plus eplerenone-treated patients) experienced impotence during the trial. Seven eplerenone-, two enalapril- and three enalapril plus eplerenone-treated patients experienced serious hyperkalemia (≥6.0 mmol/L).
Taniguchi et al.[90] (2006) Candesartan 8 mg in addition to spironolactone 25 mg QD for 6 months, after 6 months of candesartan monotherapy (combination group) vs candesartan 8 mg daily for 12 months	DB, RCT, XO Patients, 67 years of age on average, with essential HTN and left ventricular hypertrophy	N=97 1 year	Primary: Change in blood pressure and relative wall thickness Secondary: Not reported	Primary: Both study groups experienced a statistically significant reduction in blood pressure from baseline (P<0.05). While candesartan was associated with a significant reduction in relative wall thickness among patients with concentric left ventricular remodeling or hypertrophy (P<0.05), the addition of spironolactone did not provide additional benefit. Secondary: Not reported
Edwards et al.[91] (2009) Spironolactone 25 mg QD	DB, PC, RCT Patients 18 to 80 years of age with stage 2 and 3 chronic kidney	N=115 36 weeks	Primary: Change in left ventricular mass and arterial stiffness measured	Primary: Treatment with spironolactone resulted in significant reductions in left ventricular mass and left ventricular mass index. The prevalence of left ventricular hypertrophy decreased by 50% with spironolactone, but was unchanged with placebo. Spironolactone did not affect left ventricular volumes or ejection fraction.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo Study medications were added to existing ACE inhibitor or ARB therapy.	disease with controlled blood pressure (mean daytime ambulatory blood pressure <130/85 mm Hg) on and ACE inhibitors or ARB for 6 months		Secondary: Aortic distensibility, Aug AIx, blood pressure, and albuminuria	Secondary: Treatment with spironolactone resulted in a significant decrease in pulse wave velocity, central aortic pressure augmentation, Aug Ix, and Aug Ix 75. Aortic distensibility increased with the use of spironolactone compared to placebo. Treatment with spironolactone resulted in a significant decrease in office systolic blood pressure (-11 vs -5 mm Hg, P<0.05), office pulse pressure (-5 mm Hg vs -1 mm Hg, P<0.05), central systolic blood pressure (-12 mm Hg vs -4 mm Hg, P<0.01), central mean arterial pressure (-8 mm Hg vs -4 mm Hg, P<0.05), and central pulse pressure (-5 mm Hg vs -1 mm Hg, P<0.01). Office, central, and ambulatory diastolic pressures were not different between treatment groups. Treatment with spironolactone was not associated with a significant decrease in eGFR compared to placebo (-3 vs -1 mL/min/1.73 m^2, respectively; P value not significant). Treatment with spironolactone reduced albuminuria by -21 mg/mmol compared to -8 mg/mmol with placebo (P<0.05).

*Agent not available in the United States.
Drug regimen abbreviations: BID=twice daily, QD=once daily
Study regimen abbreviations: AC=active comparator, BE=blinded endpoint, DB=double blind, MA=meta analysis, MC=multicenter, OL=open label, PC=placebo controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, SB=single blind, XO=cross over
Miscellaneous abbreviations: ACE inhibitor=angiotensin converting enzyme inhibitor, ARB=angiotensin II receptor blocker, BNP=brain natriuretic peptide, CHF=congestive heart failure, CI=confidence interval, DBP=diastolic blood pressure, eGFR=estimated glomerular filtration rate, GFR=glomerular filtration rate, HCTZ=hydrochlorothiazide, HDL-C=high-density lipoprotein cholesterol, HR=hazard ratio, HTN=hypertension, KCl=potassium chloride, LDL-C=low-density lipoprotein cholesterol, LVEF=left ventricular ejection fraction, MABP=mean arterial blood pressure, MI=myocardial infarction, MRI=magnetic resonance imaging, NYHA=New York Heart Association, OR=odds ratio, PINP=procollagen type 1 N-terminal peptide, QOL=quality of life, RAAS=renin-angiotensin-aldosterone system, RR=relative risk, SBP=systolic blood pressure, T2D=type 2 diabetes, TC=total cholesterol

Additional Evidence

Dose Simplification
Ludbrook et al. evaluated the differences in blood pressure control and adverse events with spironolactone 300 to 400 mg administered either once daily or in in divided doses. Both administration schedules were associated with comparable systolic and diastolic blood pressure reductions. None of the regimens reduced the incidence of adverse effects (85% in both groups).[92]

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 9. Relative Cost of the Mineralocorticoid (Aldosterone) Receptor Antagonists

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Eplerenone	tablet	Inspra®*	$$$$$	$
Finerenone	tablet	Kerendia®	$$$$$	N/A
Spironolactone	suspension, tablet	Aldactone®*, Carospir®	$$$$$	$
Combination Products				
Spironolactone and HCTZ	tablet	Aldactazide®*	$$$$	$$

*Generic is available in at least one dosage form or strength.
HCTZ=hydrochlorothiazide

X. Conclusions

The mineralocorticoid (aldosterone) receptor antagonists, eplerenone and spironolactone, are approved for the treatment of hypertension.[3-6] Eplerenone is also indicated to improve survival in patients with left ventricular systolic dysfunction (ejection fraction ≤40%) and clinical evidence of congestive heart failure after an acute

myocardial infarction.[5] Spironolactone is approved for the management of hyperaldosteronism, hypokalemia, and edema associated with congestive heart failure, cirrhosis, or the nephrotic syndrome. It is also indicated for patients with severe heart failure (NYHA class III to IV) to increase survival, and to reduce the need for hospitalization for heart failure when used in addition to standard therapy.[3] Spironolactone is now available as an oral suspension. Of note, Carospir® is not therapeutically equivalent to Aldactone®.[4] Spironolactone is available as single entity agents, as well as in combination with hydrochlorothiazide as a fixed-dose combination product. Finerenone is a novel, non-steroidal, selective mineralocorticoid receptor antagonist indicated to reduce the risk of sustained eGFR decline, end stage kidney disease, cardiovascular death, non-fatal myocardial infarction, and hospitalization for heart failure in adult patients with CKD associated with T2D.[7] All of the mineralocorticoid (aldosterone) receptor antagonist products are available in a generic formulation except for finerenone.

There are several national and international guidelines that provide recommendations regarding the use of the mineralocorticoid (aldosterone) receptor antagonists.[10-30] For the treatment of heart failure, a mineralocorticoid (aldosterone) receptor antagonist is routinely recommended in addition to standard therapy (ACE inhibitor or ARB, and β-blocker) in patients with symptoms and an LVEF ≤35%. A mineralocorticoid (aldosterone) receptor antagonist is also recommended following a myocardial infarction in patients with an LVEF ≤40% who also have either diabetes or heart failure. Once again, therapy should be in addition to standard heart failure therapy (ACE inhibitor or ARB, and β-blocker).[18-19] There are several national and international organizations that have published guidelines on the treatment of hypertension. Most of the guidelines do not address the use of the mineralocorticoid (aldosterone) receptor antagonists. Thiazide-type diuretics are frequently recommended as initial therapy in patients with uncomplicated hypertension.[20-26] According to the National Heart, Lung, and Blood Institute's Eighth Report of The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8), thiazide-type diuretics should be utilized first-line for most patients with hypertension, either alone or in combination with another antihypertensive from a different medication class (e.g., ACE inhibitors, ARBs, β-blockers, calcium channel blockers).[20] Several guidelines consistently recommend that the selection of an antihypertensive agent be based on compelling indications for use.[20-26] Most patients will require more than one antihypertensive agent to achieve blood pressure goals.[20-26]

For the treatment of cirrhosis and ascites, spironolactone is recommended as first line therapy in addition to sodium restriction.[29] Spironolactone is also recommended for the treatment of patients with unilateral primary aldosteronism (in lieu of surgery) and in those with bilateral adrenal disease. Eplerenone is considered an alternative treatment option, especially in men who experience erectile dysfunction and gynecomastia with spironolactone therapy.[30]

For diabetic kidney disease, guidelines recommend the use of ACEIs or ARBs in patients who have CKD and albuminuria and have more recently recommended the addition of SGLT2 inhibitor. The ADA guidelines recommend a nonsteroidal mineralocorticoid receptor antagonist (finerenone) to reduce CKD progression and cardiovascular events in patients with CKD who are at increased risk for cardiovascular events or CKD progression and are unable to use a SGLT2 inhibitor.[28]

Eplerenone and spironolactone have been shown to reduce cardiovascular morbidity and mortality in patients with heart failure when added to standard therapy.[42-47,49-54] These agents have also been shown to effectively lower blood pressure.[65-86] Only one trial in hypertensive patients included both eplerenone and spironolactone. Both products significantly decreased blood pressure compared to placebo; however, statistical analyses were not performed among the two agents. The authors noted that there was a greater reduction in blood pressure with spironolactone 50 mg twice daily compared to eplerenone 50 mg twice daily. This information suggests that eplerenone may only be 50 to 75% as potent as spironolactone.[69] Most patients will require more than one antihypertensive agent to achieve blood pressure goals.[20-27] The use of a fixed-dose combination product may simplify the treatment regimen and improve adherence.[22-23,26,90] However, there are no prospective, randomized trials that have demonstrated better clinical outcomes with a fixed-dose combination product compared to the coadministration of the individual components as separate formulations. Several studies in diabetic and non-diabetic patients with renal disease have demonstrated a reduction in proteinuria with the addition of spironolactone to existing ACE inhibitor and/or ARB therapy.[31-41] Studies have demonstrated efficacy of finerenone compared to placebo in reducing incidence of composite cardiovascular outcome including time to cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure, among patients with CKD and T2D.[87,88]

In general, adverse events are similar with the mineralocorticoid (aldosterone) receptor antagonists and both agents can increase serum potassium levels. While eplerenone is a selective aldosterone receptor antagonist, spironolactone may also antagonize glucocorticoid, progesterone, and androgen receptors. Consequently, there is an increased risk of steroid-related adverse effects with spironolactone (e.g., gynecomastia, impotence, menstrual abnormalities).[1-6] Finerenone is a novel, non-steroidal, selective mineralocorticoid (aldosterone) receptor antagonists that appears to be more selective for the mineralocorticoid receptor. Finerenone has shown to reduce albuminuria in T2D patients with CKD, while revealing only a low risk of hyperkalemia.[7-9]

There is insufficient evidence to support that one brand mineralocorticoid (aldosterone) receptor antagonist is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand mineralocorticoid (aldosterone) receptor antagonists within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand mineralocorticoid (aldosterone) receptor antagonist is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Renin Inhibitors
AHFS Class 243240
May 8, 2024

I. Overview

The renin-angiotensin-aldosterone system (RAAS) is the most important component in the homeostatic regulation of blood pressure.[1] Excessive activity of the RAAS may lead to hypertension, as well as fluid and electrolyte disorders. Renin catalyzes the conversion of angiotensinogen to angiotensin I, which is the first and rate-limiting step of the RAAS.[1-3] Angiotensin I is then cleaved to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II may also be generated through other pathways (angiotensin I convertase). Through a negative feedback mechanism, angiotensin II inhibits renin release. Angiotensin II can increase blood pressure by direct vasoconstriction, as well as through actions on the brain and autonomic nervous system. In addition, angiotensin II induces aldosterone synthesis from the adrenal cortex, leading to sodium and water reabsorption. Angiotensin II exerts other detrimental effects, including ventricular hypertrophy, remodeling and myocyte apoptosis.[4,5]

Aliskiren is the only renin inhibitor that is currently available and it is approved for the treatment of hypertension. It decreases plasma renin activity and inhibits the conversion of angiotensinogen to angiotensin I. It is unknown if aliskiren affects other RAAS components, such as ACE or non-ACE pathways. Aliskiren is available as a single entity product, as well as in combination with hydrochlorothiazide.[6-7] Previously, aliskiren was available in combination with valsartan under the name Valturna®; however, this agent was removed from the market in 2012 due to evidence suggesting an increased risk of renal impairment, hypotension, and hyperkalemia in patients taking aliskiren and ACE inhibitors or ARBs concomitantly.[8] Combination products containing aliskiren and amlodipine, with or without hydrochlorothiazide, are also no longer available.

The renin inhibitors that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Aliskiren is available in a generic formulation. This class was last reviewed in May 2022.

Table 1. Renin Inhibitors Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Aliskiren	tablet	Tekturna®*	aliskiren
Combination Products			
Aliskiren and hydrochlorothiazide	tablet	Tekturna HCT®	none

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the renin inhibitors are summarized in Table 2.

Table 2. Treatment Guidelines Using the Renin Inhibitors

Clinical Guideline	Recommendations
Eighth Joint National Committee (JNC 8): **2014 Evidence-based Guideline for the Management of High Blood Pressure in Adults (2014)[9]**	• Pharmacologic treatment should be initiated in patients ≥60 years of age to lower blood pressure at systolic blood pressure ≥150 mm Hg or diastolic blood pressure ≥90 mm Hg and to a goal systolic blood pressure <150 mm Hg and goal diastolic blood pressure <90 mm Hg. Adjustment of treatment is not necessary if treatment results in lower blood pressure and treatment is well tolerated and without adverse effects on health or quality of life. • In patients <60 years of age, pharmacologic treatment should be initiated to lower blood pressure at diastolic blood pressure ≥90 mm Hg to a goal diastolic blood pressure <90 mm Hg.

Clinical Guideline	Recommendations
	• In patients <60 years of age, pharmacologic treatment should be initiated to lower blood pressure at systolic blood pressure ≥150 mm Hg to a goal diastolic blood pressure <140 mm Hg. • For patients ≥18 years of age with chronic kidney disease or diabetes, pharmacologic treatment should be initiated to lower blood pressure at systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg and to a goal systolic blood pressure <140 mm Hg and goal diastolic blood pressure <90 mm Hg. • Initial antihypertensive treatment for the general nonblack population, including those with diabetes, should include thiazide-type diuretic, calcium channel blocker (CCB), ACE inhibitor, or ARB. • Initial antihypertensive treatment for the general black population, including those with diabetes, should include thiazide-type diuretic or CCB. • For patients ≥18 years of age with chronic kidney disease regardless of race or diabetes status, initial (or add-on) treatment should include an ACE inhibitor or ARB to improve kidney outcomes. • The main goal of antihypertensive treatment is to attain and maintain goal blood pressure. • If goal blood pressure is not attained within a month of treatment, the dose of the initial drug should be increased or second drug from the thiazide-type diuretic, CCB, ACE inhibitor, or ARB classes should be added. • If goal is not achieved with two drugs, a third drug from the thiazide-type diuretic, CCB, ACE inhibitor, or ARB classes should be added. • An ACE inhibitor and ARB should not be used together. • Antihypertensive classes can be used if the patient is unable to achieve goal blood pressure with three agents or had a contraindication to a preferred class. • If blood pressure is not able to be achieved or in complicated patients, referral to a hypertension specialist may be indicated.
International Society of Hypertension: **Global Hypertension Practice Guidelines (2020)**[10]	<u>Lifestyle modifications</u> • Lifestyle modification is the first line of antihypertensive treatment. • Salt reduction: Reduce salt added when preparing foods, and at the table. Avoid or limit consumption of high salt foods such as soy sauce, fast foods and processed food including breads and cereals high in salt. • Healthy diet: Eating a diet that is rich in whole grains, fruits, vegetables, polyunsaturated fats and dairy products and reducing food high in sugar, saturated fat and trans fats, such as the DASH diet. • Healthy drinks: Moderate consumption of coffee, green and black tea. Other beverages that can be beneficial include karkadé (hibiscus) tea, pomegranate juice, beetroot juice and cocoa. • Moderation of alcohol consumption: The recommended daily limit for alcohol consumptions is 2 standard drinks for men and 1.5 for women (10 g alcohol/standard drink). Avoid binge drinking. • Weight reduction: Body weight control is indicated to avoid obesity. Particularly abdominal obesity should be managed. Ethnic-specific cut-offs for BMI and waist circumference should be used. Alternatively, a waist-to-height ratio <0.5 is recommended for all populations. • Smoking cessation: Smoking is a major risk factor for cardiovascular disease (CVD), COPD and cancer. Smoking cessation and referral to smoking cessation programs are advised. • Regular physical activity: Studies suggest that regular aerobic and resistance exercise may be beneficial for both the prevention and treatment of hypertension. Moderate intensity aerobic exercise (walking, jogging, cycling, yoga, or swimming) for 30 minutes on five to seven days per week Strength training also can help reduce blood pressure. Performance of resistance/strength exercises on two to three days per week.

Clinical Guideline	Recommendations
	• Reduce stress and induce mindfulness: Stress should be reduced and mindfulness or meditation introduced into the daily routine. • Reduce exposure to air pollution and cold temperature: Evidence from studies support a negative effect of air pollution on blood pressure in the long-term. <u>Pharmacological Treatment</u> • Ideal characteristics of drug treatment o Treatments should be evidence-based in relation to morbidity/mortality prevention. o Use a once-daily regimen which provides 24-hour blood pressure control. o Treatment should be affordable and/or cost-effective relative to other agents. o Treatments should be well-tolerated. o Evidence of benefits of use of the medication in populations to which it is to be applied. • General scheme for drug treatment o Lifestyle modification is the first line of antihypertensive treatment. o Grade 1 hypertension (BP 140 to 159/ 90 to 99): Immediate drug treatment in high-risk patients or those with CVD, chronic kidney disease (CKD), diabetes mellitus (DM), or hypertension-mediated organ damage (HMOD). Drug treatment after three to six months of lifestyle intervention if BP still not controlled in low to moderate risk patients. o Grade 2 hypertension (BP ≥160/100): Immediate drug treatment in all patients. • Core drug-treatment strategy o Step 1: Dual low-dose combination (ACE inhibitor or ARB plus dihydropyridine-calcium channel blockers (DHP-CCB)); consider monotherapy in low-risk grade 1 hypertension or in very old (≥80 years) or frail patients; consider ACE/ARB plus thiazide-like diuretic in post-stroke, very elderly, incipient HF, or CCB intolerance; consider ACE/ARB plus DHP-CCB or DHP-CCB plus thiazide-like diuretics in black patients. o Step 2: Dual full-dose combination (ACE inhibitor or ARB plus DHP-CCB); consider monotherapy in low-risk grade 1 hypertension or in very old (≥80 years) or frail patients; consider ACE/ARB plus thiazide-like diuretic in post-stroke, very elderly, incipient HF, or CCB intolerance. o Step 3: Triple combination (ACE/ARB plus DHP-CCB plus thiazide-like diuretic). o Step 4, resistant hypertension: triple combination plus spironolactone or other drug, alternatives include amiloride, doxazosin, eplerenone, clonidine, or β-blocker. Caution with spironolactone or other potassium sparing diuretics when estimated GFR <45 mL/min/1.73m^2 or K+ >4.5 mmol/L. o Consider β-blockers at any treatment step when there is a specific indications for their use, e.g., heart failure, angina, post-MI, atrial fibrillation, or younger women planning pregnancy or pregnant.
Hypertension Canada: **2020 Guidelines for the Prevention, Diagnosis, Risk Assessment, and Treatment of Hypertension in Adults and Children (2020)**[11]	<u>Indications for drug therapy for adults with hypertension without compelling indications for specific agents</u> • Antihypertensive therapy should be prescribed for average diastolic blood pressure (DBP) measurements of ≥100 mmHg or average systolic blood pressure (SBP) measurements of ≥160 mmHg in patients without macrovascular target organ damage or other cardiovascular risk factors. • Antihypertensive therapy should be strongly considered for average DPB readings ≥90 mmHg or for average SBP readings ≥140 mmHg in the presence of macrovascular target organ damage or other independent cardiovascular risk

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	factors. • For high-risk patients, aged 50 years or older, with SBP levels ≥130 mmHg, intensive management to target a SBP <120 mmHg should be considered. Patient selection for intensive management is recommended and caution should be taken in certain high-risk groups. <u>Indications for drug therapy for adults with diastolic and with or without systolic hypertension</u> • Initial therapy should be with either monotherapy or single pill combination (SPC). o Recommended monotherapy choices are: ▪ A thiazide/thiazide-like diuretic, with longer-acting diuretics preferred; ▪ A β-blocker (in patients <60 years of age); ▪ An angiotensin-converting enzyme (ACE) inhibitor (in nonblack patients); ▪ An angiotensin receptor blocker (ARB); or ▪ A long-acting calcium channel blocker (CCB). o Recommended SPC choices are those in which an ACE inhibitor is combined with a CCB, ARB with a CCB, or ACE inhibitor or ARB with a diuretic. o Hypokalemia should be avoided in patients treated with thiazide/thiazide-like diuretic monotherapy. • Additional antihypertensive drugs should be used if target BP levels are not achieved with standard-dose monotherapy. Add-on drugs should be chosen from first-line choices. Useful choices include a thiazide/thiazide-like diuretic or CCB with either: ACE inhibitor, ARB, or β-blocker. Caution should be exercised in combining a nondihydropyridine CCB and a β-blocker. The combination of an ACE inhibitor and an ARB is not recommended. • If BP is still not controlled with a combination of two or more first-line agents, or there are adverse effects, other antihypertensive drugs may be added. • Possible reasons for poor response to therapy should be considered. • α-Blockers are not recommended as first-line agents for uncomplicated hypertension; β-blockers are not recommended as first-line therapy for uncomplicated hypertension in patients ≥60 years of age; and ACE inhibitors are not recommended as first-line therapy for uncomplicated hypertension in black patients. However, these agents may be used in patients with certain comorbid conditions or in combination therapy. <u>Indications for drug therapy for adults with isolated systolic hypertension</u> • Initial therapy should be single-agent therapy with a thiazide/thiazide-like diuretic, a long-acting dihydropyridine CCB, or an ARB. If there are adverse effects, another drug from this group should be substituted. Hypokalemia should be avoided in patients treated with thiazide/thiazide-like diuretic monotherapy. • Additional antihypertensive drugs should be used if target BP levels are not achieved with standard-dose monotherapy. Add-on drugs should be chosen from first-line options. • If BP is still not controlled with a combination of two or more first-line agents, or there are adverse effects, other classes of drugs (such as α-blockers, ACE inhibitors, centrally acting agents, or nondihydropyridine CCBs) may be combined or substituted. • Possible reasons for poor response to therapy should be considered. • α-Blockers are not recommended as first-line agents for uncomplicated isolated systolic hypertension; and β-blockers are not recommended as first-line therapy for isolated systolic hypertension in patients ≥60 years of age. However, both agents may be used in patients with certain comorbid conditions or in

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	combination therapy. Guidelines for hypertensive patients with coronary artery disease (CAD) • For most hypertensive patients with CAD, an ACE inhibitor or ARB is recommended. • For hypertensive patients with CAD, but without coexisting systolic heart failure, the combination of an ACE inhibitor and ARB is not recommended. • For high-risk hypertensive patients, when combination therapy is being used, choices should be individualized. The combination of an ACE inhibitor and a dihydropyridine CCB is preferable to an ACE inhibitor and a thiazide/thiazide-like diuretic in selected patients. • For patients with stable angina pectoris but without previous heart failure, myocardial infarction, or coronary artery bypass surgery, either a β-blocker or CCB can be used as initial therapy. • Short-acting nifedipine should not be used. • When decreasing SBP to target levels in patients with established CAD (especially if isolated systolic hypertension is present), be cautious when the DBP is ≤60 mmHg because of concerns that myocardial ischemia might be exacerbated, especially in patients with left ventricular hypertrophy (LVH). Guidelines for patients with hypertension who have had a recent myocardial infarction • Initial therapy should include a β-blocker as well as an ACE inhibitor. • An ARB can be used if the patient is intolerant of an ACE inhibitor. • CCBs may be used in patients after myocardial infarction when β-blockers are contraindicated or not effective. Nondihydropyridine CCBs should not be used when there is heart failure, evidenced by pulmonary congestion on examination or radiography. Treatment of hypertension in association with heart failure • In patients with systolic dysfunction (ejection fraction <40%), ACE inhibitors and β-blockers are recommended for initial therapy. Aldosterone antagonists (mineralocorticoid receptor antagonists) may be combined in treatment for patients with a recent cardiovascular hospitalization, acute myocardial infarction, elevated B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide level, or New York Heart Association (NYHA) Class II-IV symptoms. Careful monitoring for hyperkalemia is recommended when combining an aldosterone antagonist with ACE inhibitor or ARB treatment. Other diuretics are recommended as additional therapy if needed. Beyond considerations of BP control, doses of ACE inhibitors or ARBs should be titrated to those reported to be effective in trials unless adverse effects become manifest. • An ARB is recommended if ACE inhibitors are not tolerated. • A combination of hydralazine and isosorbide dinitrate is recommended if ACE inhibitors and ARBs are contraindicated or not tolerated. • For hypertensive patients whose BP is not controlled, an ARB may be combined with an ACE inhibitor and other antihypertensive drug treatment. Careful monitoring should be used if combining an ACE inhibitor and an ARB because of potential adverse effects such as hypotension, hyperkalemia, and worsening renal function. Additional therapies may also include dihydropyridine CCBs. • An angiotensin receptor-neprilysin inhibitor (ARNI) should be used in place of an ACE inhibitor or ARB for patients with HFrEF (<40%) who remain symptomatic despite treatment with appropriate dose of guideline directed HF therapy. Eligible patients must have a serum potassium <5.2 mmol/L, an eGFR ≤30 mL/min/1.73m^2 and close surveillance of serum potassium and creatinine.

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	Treatment of hypertension in association with stroke
	• BP management in acute ischemic stroke (onset to 72 hours)
	  o Please refer to Stroke Best Practice recommendations.
	• BP management after acute ischemic stroke
	  o Strong consideration should be given to the initiation of antihypertensive therapy after the acute phase of a stroke or transient ischemic attack.
	  o After the acute phase of a stroke, BP-lowering treatment is recommended to a target of consistently <140/90 mmHg.
	  o Treatment with an ACE inhibitor and thiazide/thiazide-like diuretic combination is preferred.
	  o For patients with stroke, the combination of an ACE inhibitor and ARB is not recommended.
	• BP management in hemorrhagic stroke (onset to 72 hours)
	  o Please refer to Stroke Best Practice recommendations.
	
	Treatment of hypertension in association with LVH
	• Hypertensive patients with LVH should be treated with antihypertensive therapy to decrease the rate of subsequent cardiovascular events.
	• The choice of initial therapy can be influenced by the presence of LVH. Initial therapy can be drug treatment using ACE inhibitors, ARBs, long-acting CCBs, or thiazide/thiazide-like diuretics. Direct arterial vasodilators such as hydralazine or minoxidil should not be used.
	
	Treatment of hypertension in association with nondiabetic chronic kidney disease
	• Individualize BP targets in patients with chronic kidney disease. Consider intensive targets (SBP <120 mmHg) in appropriate patients.
	• For patients with hypertension and proteinuric chronic kidney disease (urinary protein >150 mg per 24 hours or albumin to creatinine ratio >30 mg/mmol), initial therapy should be an ACE inhibitor or an ARB if there is intolerance to ACE inhibitors.
	• In most cases, combination therapy with other antihypertensive agents might be needed to reach target BP levels.
	• The combination of an ACE inhibitor and ARB is not recommended for patients with nonproteinuric chronic kidney disease.
	
	Treatment of hypertension in association with renovascular disease
	• Patients with hypertension attributable to atherosclerotic renal artery stenosis should be primarily medically managed because renal angioplasty and stenting offers no benefit over optimal medical therapy alone.
	• Renal artery angioplasty and stenting for atherosclerotic hemodynamically significant renal artery stenosis could be considered for patients with uncontrolled hypertension resistant to maximally tolerated pharmacotherapy, progressive renal function loss, and acute pulmonary edema.
	• Patients with confirmed renal fibromuscular dysplasia (FMD) should be referred to a hypertension specialist.
	• Renal artery angioplasty without stenting is recommended for treatment of FMD-related renal artery stenosis. Stenting is not recommended unless needed because of a periprocedural dissection. Surgical revascularization should be considered in cases of complex lesions less amendable to angioplasty, stenosis associated with complex aneurysm, and restenosis despite two unsuccessful attempts of angioplasty.
	
	Treatment of hypertension in association with diabetes mellitus
	• Persons with diabetes mellitus should be treated to attain SBP of <130 mmHg and DBP of <80 mmHg.

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	• For persons with cardiovascular or kidney disease, including microalbuminuria, or with cardiovascular risk factors in addition to diabetes and hypertension, an ACE inhibitor or an ARB is recommended as initial therapy. • For persons with diabetes and hypertension not included in other guidelines in this section, appropriate choices include (in alphabetical order): ACE inhibitors, ARBs, dihydropyridine CCBs, and thiazide/thiazide-like diuretics. • If target BP levels are not achieved with standard-dose monotherapy, additional antihypertensive therapy should be used. For persons in whom combination therapy with an ACE inhibitor is being considered, a dihydropyridine CCB is preferable to a thiazide/thiazide-like diuretic. <u>Resistant hypertension</u> • Resistant hypertension is defined as BP above target despite three or more BP-lowering drugs at optimal doses preferably including a diuretic (and usually a renin-angiotensin-aldosterone system blocker and a CCB. • Accurate office and out-of-office BP measurement is essential. • Other reasons for apparent resistant hypertension should be eliminated before diagnosing true resistant hypertension, including nonadherence, white coat effect, and secondary hypertension. • Pharmacotherapy with the additional use of spironolactone, bisoprolol, doxazosin, amiloride, eplerenone, or clonidine with the baseline regimen decreases BP significantly, with the greatest BP-lowering shown with spironolactone. • Patients with resistant hypertension should be referred to providers with expertise in diagnosis and management of hypertension. <u>Hypertension and pediatrics</u> • BP should be measured regularly in children three years of age or older; the auscultatory method is the gold-standard at present. • Initial therapy should be monotherapy, with an ACE inhibitor or ARB (not first-line in black children), or a long-acting dihydropyridine CCB. • The treatment t goal is systolic and diastolic office BP and/or ABPM < 95th percentile or <90th percentile in children with risk factors or target organ damage. • Complex cases should be referred to an expert in pediatric hypertension. <u>Hypertension and pregnancy</u> • Up to 7% of pregnancies are complicated by a hypertensive disorder of pregnancy, and approximately 5% of women will have chronic hypertension when they become pregnant. • The prevalence of hypertension in pregnancy is expected to increase with women becoming pregnant later in their reproductive years and the increasing prevalence of cardiovascular comorbidities such as increased preconception body mass index and maternal diabetes. • The possibility of pregnancy should be considered when managing women with hypertension who are of reproductive age. • Preconception counselling should be offered to all women with hypertension who are considering pregnancy. • ACE inhibitor and ARB therapy should be avoided before conception and during pregnancy unless there is a compelling indication for their use (i.e., proteinuric kidney disease). • Hypertension during pregnancy can increase the risk of adverse maternal and fetal outcomes, including an increased risk of preeclampsia, placental abruption, prematurity, small for gestational age infants, stillbirth, and maternal renal and retinal injury, thus generally requires involvement of an interdisciplinary team including obstetrical care providers.

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	• Antihypertensive therapy is recommended for average SBP measurements of ≥140 mmHg or DBP measurements of ≥90 mmHg in pregnant women with chronic hypertension, gestational hypertension, or preeclampsia. Initial antihypertensive therapy should be monotherapy from the following first-line drugs: oral labetalol, oral methyldopa, long-acting oral nifedipine, or other oral b-blockers (acebutolol, metoprolol, pindolol, and propranolol). Other antihypertensive drugs can be considered as second-line drugs including: clonidine, hydralazine, and thiazide diuretics. • Women with severe hypertension with SBP ≥160 mmHg or DBP ≥110 mmHg in pregnancy or postpartum require urgent antihypertensive therapy because it is considered an obstetrical emergency. • Antihypertensive drugs used in breastfeeding women include: labetalol, methyldopa, long-acting nifedipine, enalapril, or captopril.
European Society of Hypertension: **2023 Guidelines for the management of arterial hypertension (2023)**[12]	General recommendations for antihypertensive drug treatment • BP lowering should be prioritized over the selection of specific antihypertensive drug classes because treatment benefit largely originates from BP reduction. • Five major drug classes including, ACE inhibitors, ARBs, β-blockers, CCBs, and Thiazide/Thiazide-like diuretics have effectively reduced blood pressure and cardiovascular events in randomized controlled trials. These drugs and their combinations are recommended as the basis of antihypertensive treatment strategies. • Initiation of therapy with a two-drug combination is recommended for most hypertensive patients. Preferred combinations should comprise a RAS blocker (either an ACE inhibitor or an ARB) with a CCB or thiazide/thiazide-like diuretic. Other combinations of the five major drug classes can be used. • Initiation with monotherapy can be considered in patients with: grade 1 hypertension and low-risk if BP is only marginally elevated (less than 150 mmHg SBP and 95 mmHg DBP) high-normal BP and very high cardiovascular risk, frailty and/or and advance age. • If BP is not controlled with the initial two-drug combination by using the maximum recommended and tolerated dose of the respective components, treatment should be increased to a three-drug combination, usually a RAS blocker plus CCB plus thiazide/thiazide-like diuretic. • If BP is not controlled with a three-drug combination by using the maximum recommended and tolerated dose of the respective components, it is recommended to extend treatment according to the recommendations for resistant hypertension. • The use of single pill combinations should be preferred at any treatment step (i.e. during initiation of therapy with a two-drug combination and at any other step of treatment). • β-blocker should be used at initiation of therapy or at any treatment step as guideline-directed medical therapy (e.g., heart failure with reduced ejection fraction, anti-ischemic therapy in chronic coronary syndromes, heart rate control in atrial fibrillation). • β-blockers can be considered in the presence of several other conditions in which their use can be favorable. • The combination of two RAS blockers is not recommended due to increased risk of adverse events, in particular AKI. True-resistant hypertension • In resistant hypertension, it is recommended to reinforce lifestyle measures. • Drugs that can be considered as additional therapy in patients with resistant hypertension are preferably spironolactone (or other MRA), or β-blocker or Alpha-1 blockers or centrally acting agents (clonidine), or amiloride. • Thiazide/thiazide-like diuretics are recommended in resistant hypertension if

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	estimated eGFR is ≥30 mL/min/1.73m^2. • Loop diuretics may be considered in patients with an estimated eGFR < 45 mL/min/1.73m^2 and should be used if eGFR falls below 30 mL/min/1.73m^2. • Chlorthalidone (12.5 to 25 mg once daily) could be used with or without a loop diuretic if eGFR is <30 mL/min/1.73m^2. • Renal deprivation can be considered as an additional treatment option in patients with resistant hypertension if eGFR is >40 mL/min/1.73m^2. • Patients with resistant hypertension should be followed very closely. Follow-up includes periodical ambulatory blood pressure monitoring and assessment of hypertension-mediated organ damage, particularly kidney function and serum potassium levels. Regular use of home blood pressure monitoring and monitoring of drug adherence are desirable.
National Institute for Health and Clinical Excellence: **Hypertension in adults: diagnosis and management (2019)**[13]	<u>Choosing antihypertensive drug treatment (for people with or without type II diabetes)</u> • Where possible, recommend treatment with drugs taken only once a day. • Prescribe non-proprietary drugs where these are appropriate and minimize cost. • Offer people with isolated systolic hypertension (systolic blood pressure ≥160 mmHg) the same treatment as people with both raised systolic and diastolic blood pressure. • Offer antihypertensive drug treatment to women of child-bearing potential with diagnosed hypertension in line with recommendations in this guideline. For women considering pregnancy or who are pregnant or breastfeeding, manage hypertension in line with the recommendations on Management of pregnancy with chronic hypertension and Breastfeeding in 'Hypertension in pregnancy'. • When choosing antihypertensive drug treatment for adults of black African or African-Caribbean family origin, consider an angiotensin II receptor blocker, in preference to an angiotensin-converting enzyme inhibitor. <u>Step one treatment</u> • Patients <55 years of age should be offered a step one antihypertensive with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). • Offer an ACE inhibitor or an ARB to adults starting step 1 antihypertensive treatment who have type II diabetes and are of any age or family origin or those aged <55 years but not of black African or African-Caribbean family origin. • If an ACE inhibitor is not tolerated, offer an ARB. • Do not combine an ACE inhibitor with an ARB for the treatment of hypertension. • Offer a calcium channel blocker (CCB) to adults starting step 1 antihypertensive treatment who are >55 years of age and do not have diabetes and are of black African or African-Caribbean family origin and do not have type II diabetes and of any age. • If a CCB is not suitable, for example because of edema or intolerance, or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic. • If diuretic treatment is to be initiated or changed, offer a thiazide‑like diuretic, such as indapamide in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide. • For adults with hypertension who are already receiving treatment with bendroflumethiazide or hydrochlorothiazide, who have stable, well-controlled blood pressure, continue with their treatment. <u>Step two treatment</u> • Before considering next step treatment for hypertension discuss with the person

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	if they are taking their medicine as prescribed and support adherence in line with NICE's guideline on "Medicines adherence: involving patients decisions about prescribed medicines and supporting adherence". • If hypertension is not controlled with a step one treatment of an ACE inhibitor or ARB, offer choice of one of the following drugs in addition to the step one treatment: a CCB or a thiazide-like diuretic. • If hypertension is not controlled in adults taking step one treatment of a CCB, offer the choice of one of the following drugs in addition to the step one treatment: an ACE inhibitor or an ARB or a thiazide-like diuretic. • If hypertension is not controlled in adults of black African or African–Caribbean family origin who do not have type 2 diabetes taking step one treatment, consider an ARB, in preference to an ACE inhibitor, in addition to step one treatment. <u>Step three treatment</u> • Before considering step three treatment, review the person's medications to ensure they are being taken at the optimal doses and discuss adherence (see recommendation under step two). • If hypertension is not controlled in adults taking step two treatment, offer a combination of an ACE inhibitor or ARB and a CCB and a thiazide-like diuretic. <u>Step four treatment</u> • If hypertension is not controlled in adults taking the optimal tolerated doses of an ACE inhibitor or an ARB plus a CCB and a thiazide-like diuretic, regard them as having resistant hypertension. • Before considering further treatment for a person with resistant hypertension, confirm elevated clinic blood pressure measurements using ambulatory or home blood pressure recordings, assess for postural hypotension, and discuss adherence. • For people with confirmed resistant hypertension, consider adding a fourth antihypertensive drug as step four treatment or seeking specialist advice. • Consider further diuretic therapy with low-dose spironolactone for adults with resistant hypertension starting step four treatment who have a blood potassium level of 4.5 mmol/l or less. Use particular caution in people with a reduced estimated glomerular filtration rate because they have an increased risk of hyperkalemia. • When using further diuretic therapy for step four treatment of resistant hypertension, monitor blood sodium and potassium and renal function within one month of starting treatment and repeat as needed thereafter. • Consider an alpha-blocker or beta-blocker for adults with resistant hypertension starting step four treatment who have a blood potassium level of more than 4.5 mmol/l. • If blood pressure remains uncontrolled in people with resistant hypertension taking the optimal tolerated doses of four drugs, seek specialist advice.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in Blacks (2010)[14]**	• To attain and maintain blood pressure (BP) below target levels, multiple antihypertensive drugs will be required in most hypertensive blacks. • Use of two-drug combination therapy when SBP is >15 mm Hg and/or DBP is >10 mm Hg above goal levels is increasingly recommended as first-line therapy. • Two-drug regimens have generally contained a thiazide-type diuretic; however, the combination of a calcium channel blocker (CCB) with either an ACE inhibitor or an ARB has been shown equally efficacious in BP lowering but with demonstrated superiority (CCB+ACE) for hard clinical outcomes compared with the same ACE inhibitor plus a thiazide-type diuretic. • In secondary prevention patients, the combination therapy should include a drug(s) with the appropriate compelling indications.

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	• Certain classes of antihypertensive medications, specifically diuretics and CCBs, lower BP on average more than β-blockers and renin-angiotensin system (RAS) blockers in black patients when used as monotherapies. • In the absence of compelling indications, when BP is near goal levels, monotherapy with a diuretic or a CCB is preferred. • Lifestyle modifications should be initiated in all patients with hypertension, whether or not pharmacotherapy is planned. • ACE inhibitors or ARBs are recommended as alternative monotherapy options in the treatment of hypertension in blacks. The rationale for their lower tier monotherapy recommendation is because they have consistently achieved lesser average reductions in BP relative to that observed with monotherapy using either a diuretic or CCB.
Kidney Disease Improving Clinical Outcomes Group: **KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease (2021)**[15]	<u>Blood pressure measurement</u> • The Work Group recommends standardized office blood pressure (BP) measurement in preference to routine office BP measurements for the management of high BP in adults. • The Work Group suggests that out-of-office BP measurements with ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM) be used to complement standardized office BP readings for the management of high BP. <u>Lifestyle interventions for lowering BP in patients with chronic kidney disease (CKD) not receiving dialysis</u> • The Work Group suggests targeting a sodium intake <2 grams of sodium per day (or <90 mmol of sodium per day, or <5 grams of sodium chloride per day) in patients with high BP and CKD. • The Work Group suggests that patients with high BP and CKD be advised to undertake moderate-intensity physical activity for a cumulative duration of at least 150 minutes per week, or to a level compatible with their cardiovascular and physical tolerance. <u>BP management in patients with CKD, with or without diabetes, not receiving dialysis</u> • The Work Group suggests that adults with high BP and CKD be treated with a target systolic BP (SBP) of <120 mmHg, when tolerated, using standardized office BP measurement. • The Work Group recommends starting renin-angiotensin-system inhibitors (RASi) (angiotensin-converting enzyme inhibitor [ACEi] or angiotensin II receptor blocker [ARB]) for people with high BP, CKD, and severely increased albuminuria without diabetes. • The Work Group suggests starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately increased albuminuria without diabetes. • The Work Group recommends starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately-to-severely increased albuminuria with diabetes. • The Work Group recommends avoiding any combination of ACEi, ARB, and direct renin inhibitor (DRI) therapy in patients with CKD, with or without diabetes. <u>BP management in kidney transplant recipients</u> • Treat adult kidney transplant recipients with high BP to a target BP of <130 mmHg systolic and <80 mmHg diastolic using standardized office BP measurement. • The Work Group recommends that a dihydropyridine calcium channel blocker (CCB) or an ARB be used as the first-line antihypertensive agent in adult kidney transplant recipients.

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	BP management in children with CKD • The Work Group suggests that in children with CKD, 24-hour mean arterial pressure by ABPM should be lowered to <50th percentile for age, sex, and height.
American College of Cardiology/ American Heart Association Task Force: **Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults (2017)[16]**	Initiation of Blood Pressure (BP) Treatment for Overall Cardiovascular Disease (CVD) Risk • Use of BP-lowering medications is recommended for secondary prevention of recurrent CVD events in patients with clinical CVD and an average systolic blood pressure (SBP) ≥130 mmHg or an average diastolic blood pressure (DBP) of ≥80 mmHg and for primary prevention in adults with an estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk of ≥10% and an average SBP of ≥130 mmHg or an average ≥80 mmHg. • Use of BP-lowering medication is recommended for primary prevention of CVD in adults with no history of CVD and with an estimated 10-year ASCVD risk <10% and an SBP of ≥140 mmHg or a DBP of ≥90 mmHg. • Simultaneous use of an angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), and/or renin inhibitor is potentially harmful and is not recommended to treat adults with hypertension. • For adults with confirmed hypertension and known CVD or 10-year ASCVD risk of ≥10%, a BP target <130/80 mmHg is recommended. For adults with confirmed hypertension without additional markers of increased CVD risk, a BP target <130/80 mmHg may be reasonable. • For initiation of antihypertensive drug therapy, first-line agents include thiazide diuretics, calcium channel blockers (CCBs), and ACE inhibitors or ARBs. • Initiation of antihypertensive drug therapy with two first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended in adults with stage 2 hypertension and an average BP >20/10 mmHg above their BP target. • Initiation of antihypertensive drug therapy with a single antihypertensive drug is reasonable in adults with stage 1 hypertension and BP goal <130/80 mmHg with dosage titration and sequential addition of other agents to achieve the BP target. Stable Ischemic Heart Disease (SIHD) • In adults with SIHD and hypertension, a BP target <130/80 is recommended. • Adults with SIHD and hypertension (BP ≥130/80 mmHg) should be treated with medications [e.g., guideline-directed medical therapy (GDMT) beta-blockers, ACE inhibitors, or ARBs] for compelling indications [e.g., previous myocardial infarction (MI), stable angina] as first-line therapy, with the addition of other drugs (e.g., dihydropyridine CCBs, thiazide diuretics, and/or mineralocorticoid receptor antagonists) as needed to further control hypertension. • In adults with SIHD with angina and persistent uncontrolled hypertension, the addition of dihydropyridine CCBs to GDMT beta-blockers is recommended. • In adults who have had a MI or acute coronary syndrome, it is reasonable to continue GDMT beta-blockers beyond three years as long-term therapy for hypertension. • Beta-blockers and/or CCBs might be considered to control hypertension in patients with coronary artery disease (CAD) had an MI more than three years ago and have angina. Heart Failure • In adults with increased risk of HF, the optimal BP in those with hypertension should be <130 mmHg. • Adults with HFrEF and hypertension should be prescribed GDMT titrated to attain a BP <130/80 mmHg. • Non-dihydropyridine CCBs are not recommended in the treatment of hypertension in adults with HFrEF.

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	• In adults with HFpEF who present with symptoms of volume overload, diuretics should be prescribed to control hypertension. • Adults with HFpEF and persistent hypertension after management of volume overload should be prescribed ACE inhibitors or ARBs and beta-blockers titrated to attain SBP <130 mmHg. CKD • Adults with hypertension and CKD should be treated to a BP goal <130/80 mmHg. • In adults with hypertension and CKD [stage 3 or higher or stage 1 or 2 with albuminuria (≥300 mg/d, or ≥300 mg/g albumin-to-creatinine ratio or the equivalent in the first morning void)], treatment with an ACE inhibitor is reasonable to slow kidney disease progression. Treatment with an ARB may be reasonable if an ACE inhibitor is not tolerated. • After kidney transplantation, it is reasonable to treat patients with hypertension to a BP goal <130/80 mmHg and with a CCB on the basis of improved glomerular filtration rate (GFR) and kidney survival. Cerebrovascular Disease • In adults with intracerebral hemorrhage (ICH) who present with SBP >220 mmHg, it is reasonable to use continuous intravenous (IV) drug infusion and close BP monitoring to lower levels. Immediate lowering of SBP to <140 mmHg in adults with spontaneous ICH who present within six hours of the acute event and have an SBP between 150 mmHg and 220 mmHg is not of benefit to reduce death or severe disability and can be potentially harmful. • Adults with acute ischemic stroke and elevated BP who are eligible for treatment with IV tissue plasminogen activator (tPA) should have their BP slowly lowered to <185/110 mmHg before thrombolytic therapy is initiated. • In adults with an acute ischemic stroke, BP should be <185/110 mmHg before administration of IV tPA and should be maintained below 180/105 mmHg for at least the first 24 hours after initiation drug therapy. • Starting or restarting antihypertensive therapy during hospitalization in patients with BP >140/90 mmHg who are neurologically stable is safe and reasonable to improve long-term BP control, unless contraindicated. • In patient with BP ≥220/120 mmHg who did not receive IV alteplase or endovascular treatment and have no comorbid conditions requiring acute antihypertensive treatment, the benefit of initiating or reinitiating treatment of hypertension within the first 48 to 72 hours is uncertain. It might be reasonable to lower BP by 15% during the first 24 hours after onset of stroke. In patients with BP <220/120 mmHg with the same conditions, initiating or reinitiating treatment of hypertension within the first 48 to 72 hours after an acute ischemic stroke is not effective to prevent death or dependency. • Adults with previously treated stroke or transient ischemic attack should be restarted on antihypertensive treatment after the first few days of the index event to reduce the risk of recurrent stroke and other vascular events. Treatment with a thiazide diuretic, ACE inhibitor, or ARB, or combination treatment consisting of a thiazide diuretic plus ACE inhibitor, is useful. • Adults not previously treated for hypertension who experienced a stroke or transient ischemic attack and have an established BP ≥140/90 mmHg should be prescribed antihypertensive treatment a few days after the index event to reduce the risk of recurrent stroke and other vascular event. • For adults who experience a stroke or transient ischemic attack, selection of specific drugs should be individualized on the basis of patient comorbidities and agent pharmacological class. • For adults who experience a stroke or transient ischemic attack, a BP goal

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	<130/80 mmHg may be reasonable. • For adults with a lacunar stroke, a target SBP goal <130 mmHg may be reasonable. • In adults previously untreated for hypertension who experience an ischemic stroke or transient ischemic attack and have an SBP <140 mmHg and a DBP <90 mmHg, the usefulness of initiating antihypertensive treatment is not well established. <u>Peripheral Artery Disease (PAD)</u> • Adults with hypertension and PAD should be treated similarly to patients with hypertension without PAD. <u>Diabetes Mellitus (DM)</u> • In adults with DM and hypertension, antihypertensive drug treatment should be initiated at a BP of ≥130/80 mmHg with a treatment goal <130/80 mmHg. • In adults with DM and hypertension, all first-line classes of antihypertensive agents (i.e., diuretics, ACE inhibitors, ARBs, and CCBs) are useful and effective. • In adults with DM and hypertension, ACE inhibitors or ARBs may be considered in the presence of albuminuria. <u>Atrial Fibrillation, Valvular Heart Disease, and Aortic disease</u> • Treatment of hypertension can be useful for prevention of recurrence of AF. • In adults with asymptomatic aortic stenosis, hypertension should be treated with pharmacotherapy, starting at a low dose and gradually titrating upward as needed. • In patients with chronic aortic insufficiency, treatment of systolic hypertension with agents that do not slow the heart rate (i.e., avoid beta-blockers) is reasonable. • Beta-blockers are recommended as the preferred antihypertensive agents in patients with hypertension and thoracic aortic disease. <u>Racial and Ethnic Differences in Treatment</u> • In black adults with hypertension but without HF or CKD, including those with DM, initial antihypertensive treatment should include a thiazide-type diuretic or CCB. Two or more antihypertensive medications are recommended to achieve a BP target <130/80 mmHg in most adults with hypertension, especially in black adults with hypertension. <u>Pregnancy</u> • Women with hypertension who become pregnant, or are planning to become pregnant, should be transitioned to methyldopa, nifedipine, and/or labetalol during pregnancy. • Women with hypertension who become pregnant should not be treated with ACE inhibitors, ARBs, or direct renin inhibitors. <u>Older Persons</u> • Treatment of hypertension with an SBP treatment goal <130 mmHg is recommended for noninstitutionalized ambulatory community-dwelling adults (≥65 years of age) with an average SBP of ≥130 mmHg. • For older adults (≥65 years of age) with hypertension and a higher burden of comorbidity and limited life expectancy, clinical judgment, patient preference, and a team-based approach to assess risk/benefit is reasonable for decisions regarding intensity of BP lowering and choice of antihypertensive drugs. <u>Hypertensive Crises</u> • In adults with a hypertensive emergency, admission to an intensive care unit is

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	recommended for continuous monitoring of BP and target organ damage and for parenteral administration of an appropriate agent. • For adults with a compelling condition (i.e., aortic dissection, severe pre-eclampsia or eclampsia, or pheochromocytoma crisis), SBP should be reduced to <140 mmHg during the first hour and to <120 mmHg in aortic dissection. • For adults without a compelling condition, SBP should be reduced by no more than 25% within the first hours; then, if stable, to 160/100 mmHg within the next two to six hours; and then cautiously to normal during the following 24 to 48 hours. Cognitive Decline and Dementia • In adults with hypertension, BP lowering is reasonable to prevent cognitive decline and dementia. Patients Undergoing Surgical Procedures • In patients with hypertension undergoing major surgery who have been on beta-blockers chronically, beta-blockers should be continued. • In patients with hypertension undergoing planned elective major surgery, it is reasonable to continue medical therapy for hypertension until surgery. • In patients with hypertension undergoing major surgery, discontinuation of ACE inhibitors or ARBs perioperatively may be considered. • In patients with planned elective major surgery and SBP ≥180 mmHg or DBP ≥110 mmHg, deferring surgery may be considered. • For patients undergoing surgery, abrupt pre-operative discontinuation of beta-blockers or clonidine is potentially harmful. • Beta-blockers should not be started on the day of surgery in beta-blocker-naïve patients. • Patients with intraoperative hypertension should be managed with IV medications until such time as oral medications can be resumed.
American Diabetes Association: **Standards of Medical Care in Diabetes (2023)**[17]	Hypertension/blood pressure control • Blood pressure should be measured at every routine visit. When possible, patients found to have elevated blood pressure (systolic blood pressure 120 to 129 mmHg and diastolic <80 mmHg) should have blood pressure confirmed using multiple readings, including measurements on a separate day, to diagnose hypertension. Patients with blood pressure ≥180/110 and cardiovascular disease could be diagnosed with hypertension at a single visit. • All hypertensive patients with diabetes should monitor their blood pressure at home. • For patients with diabetes and hypertension, blood pressure targets should be individualized through a shared decision-making process that addresses cardiovascular risk, potential adverse effects of antihypertensive medications, and patient preferences. • Individuals with diabetes and hypertension qualify for antihypertensive drug therapy when the blood pressure is persistently elevated ≥130/80 mmHg. The on-treatment target blood pressure goal is <130/80 mmHg, if it can be safely attained. • In pregnant patients with diabetes and preexisting hypertension, a blood pressure target of 110 to 135/85 is suggested in the interest of reducing the risk for accelerated maternal hypertension and minimizing impaired fetal growth. • For patients with blood pressure >120/80, lifestyle intervention consists of weight loss when indicated, a Dietary Approaches to Stop Hypertension (DASH)-style eating pattern including reducing sodium and increasing potassium intake, moderation of alcohol intake, and increased physical activity. • Patients with confirmed office-based blood pressure ≥130/80 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of

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	pharmacologic therapy to achieve blood pressure goals. • Patients with confirmed office-based blood pressure ≥160/100 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of two drugs or a single pill combination of drugs demonstrated to reduce cardiovascular events in patients with diabetes. • Treatment for hypertension should include drug classes demonstrated to reduce cardiovascular events in patients with diabetes (ACE inhibitors, angiotensin receptor blockers, thiazide-like diuretics, or dihydropyridine calcium channel blockers). ACE inhibitors or angiotensin receptor blockers are recommended first-line therapy for hypertension in people with diabetes and coronary artery disease. • Multiple-drug therapy is generally required to achieve blood pressure targets (but not a combination of ACE inhibitors and angiotensin receptor blockers). • An ACE inhibitor or angiotensin receptor blocker, at the maximum tolerated dose indicated for blood pressure treatment, is the recommended first-line treatment for hypertension in patients with diabetes and urinary albumin–to–creatinine ratio ≥300 mg/g creatinine or 30 to 299 mg/g creatinine. If one class is not tolerated, the other should be substituted. • For patients treated with an ACE inhibitor, angiotensin receptor blocker, or diuretic, serum creatinine/estimated glomerular filtration rate and serum potassium levels should be monitored at least annually. • Patients with hypertension who are not meeting blood pressure targets on three classes of antihypertensive medications (including a diuretic) should be considered for mineralocorticoid receptor antagonist therapy. <u>Chronic kidney disease</u> • At least once a year, assess urinary albumin (e.g., spot urinary albumin–to–creatinine ratio) and estimated glomerular filtration rate in patients with type 1 diabetes with duration of five or more years and in all patients with type 2 diabetes. • In people with established diabetic kidney disease, urinary albumin (e.g., spot urinary albumin-to-creatinine ratio) and estimated glomerular filtration rate should be monitored one to four times per year depending on the stage of the disease. Optimize glucose control to reduce the risk or slow the progression of chronic kidney disease (CKD). • For patients with type 2 diabetes and diabetic kidney disease, use of a sodium-glucose cotransporter 2 inhibitor in patients with an estimated glomerular filtration rate ≥20 mL/min/1.73 m^2 and urinary albumin ≥200 mg/g creatinine is recommended to reduce CKD progression and cardiovascular events. • For patients with type 2 diabetes and diabetic kidney disease, use of a sodium–glucose cotransporter 2 inhibitor is recommended to reduce chronic kidney disease progression and cardiovascular events in patients with an estimated glomerular filtration rate ≥20 mL/min/1.73 m^2 and urinary albumin ranging from normal to 200 mg/g creatinine. • In people with type 2 diabetes and diabetic kidney disease, consider use of sodium–glucose cotransporter 2 inhibitors (if estimated glomerular filtration rate is ≥20 mL/min/1.73 m^2), a glucagon-like peptide 1 agonist, or a nonsteroidal mineralocorticoid receptor antagonist (if estimated glomerular filtration rate is ≥25 mL/min/1.73 m^2) additionally for cardiovascular risk reduction. • In people with chronic kidney disease and albuminuria who are at increased risk for cardiovascular events or chronic kidney disease progression, a nonsteroidal mineralocorticoid receptor antagonist shown to be effective in clinical trials is recommended to reduce chronic kidney disease progression and cardiovascular events. • Optimize blood pressure control and reduce blood pressure variability to reduce

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	the risk or slow the progression of CKD. • Do not discontinue renin-angiotensin system blockade for minor increases in serum creatinine (≤30%) in the absence of volume depletion. • For people with nondialysis-dependent stage 3 or higher CKD, dietary protein intake should be a maximum of 0.8 g/kg body weight per day (the recommended daily allowance). For patients on dialysis, higher levels of dietary protein intake should be considered, since protein energy wasting is a major problem in some dialysis patients. • In nonpregnant patients with diabetes and hypertension, either an ACE inhibitor or an angiotensin receptor blocker is recommended for those with modestly elevated urinary albumin–to–creatinine ratio (30 to 299 mg/g creatinine) and is strongly recommended for those with urinary albumin–to–creatinine ratio ≥300 mg/g creatinine and/or estimated glomerular filtration rate <60 mL/min/1.73 m^2. • Periodically monitor serum creatinine and potassium levels for the development of increased creatinine and hyperkalemia when ACE inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists are used, or hypokalemia when diuretics are used. • An ACE inhibitor or an angiotensin receptor blocker is not recommended for the primary prevention of CKD in patients with diabetes who have normal blood pressure, normal urinary albumin–to–creatinine ratio (<30 mg/g creatinine), and normal estimated glomerular filtration rate. • Patients should be referred for evaluation by a nephrologist if they have continuously increasing urinary albumin levels and/or continuously decreasing estimated glomerular filtration rate and an estimated glomerular filtration rate <30 mL/min/1.73 m^2. • Promptly refer to a nephrologist for uncertainty about the etiology of kidney disease, difficult management issues, and rapidly progressing kidney disease. •

III. Indications

The Food and Drug Administration (FDA)-approved indications for the renin inhibitors are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Renin Inhibitors[4-7]

Indication(s)	Single Entity Agents	Combination Products
	Aliskiren	Aliskiren and HCTZ
Hypertension		
Treatment of hypertension	✔	✔

HCTZ=hydrochlorothiazide

IV. Pharmacokinetics

The pharmacokinetic parameters of the renin inhibitors are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Renin Inhibitors[5]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Aliskiren	2.5	47 to 51	Liver, minor (% not reported)	Feces (91) Renal (<1)	40
Combination Products					
Aliskiren and HCTZ	2.5/50 to 75	47 to 51/ 40 to 68	Liver, minor (% not reported)/ Not reported	Feces (91) Renal (<1)/ Renal (>95)	40/6 to 15

HCTZ=hydrochlorothiazide

V. Drug Interactions

Major drug interactions with the renin inhibitors are listed in Table 5.

Table 5. Major Drug Interactions with the Renin Inhibitors[5]

Generic Name(s)	Interaction	Mechanism
Renin Inhibitors (aliskiren)	ACE inhibitors	Aliskiren is contraindicated in patients with diabetes who are receiving ARBs or ACEIs because of the increased risk of renal impairment, hyperkalemia, and hypotension. In general, avoid combined use of aliskiren with ACE inhibitors or ARBs, particularly in patients with creatinine clearance (CrCl) <60 mL/min.
Renin Inhibitors (aliskiren)	ARBs	Aliskiren is contraindicated in patients with diabetes who are receiving ARBs or ACEIs because of the increased risk of renal impairment, hyperkalemia, and hypotension. In general, avoid combined use of aliskiren with ACE inhibitors or ARBs, particularly in patients with CrCl <60 mL/min.
Renin Inhibitors (aliskiren)	Azole antifungals	Increased absorption of aliskiren resulting from inhibition of P-gp expression by certain azole antifungal agents may occur. In addition, azole antifungal agents may inhibit aliskiren metabolism (CYP3A4).
Renin Inhibitors (aliskiren)	Cyclosporine	Concurrent use of aliskiren and cyclosporine may result in increased aliskiren exposure and plasma concentrations.
Thiazide diuretics (HCTZ)	Dofetilide	Thiazide diuretics may induce hypokalemia and increase the risk of torsades de pointes.
Thiazide diuretics (HCTZ)	Lithium	Decreased lithium clearance may occur with thiazide use, which may lead to increased serum lithium levels and possibly lithium toxicity.
Thiazide diuretics (HCTZ)	Diazoxide	The combination of diazoxide with a thiazide diuretic may lead to hyperglycemia, hyperuricemia, and hypotension.
Thiazide diuretics (HCTZ)	Digitalis glycosides	Thiazide diuretics may induce electrolyte disturbances which may predispose patients to digitalis-induced arrhythmias.

ACE inhibitor=angiotensin converting enzyme inhibitor, ARB=angiotensin II receptor antagonist

VI. Adverse Drug Events

The most common adverse drug events reported with the renin inhibitors are listed in Table 6. The boxed warning for aliskiren-containing products is listed in Table 7.

Table 6. Adverse Drug Events (%) Reported with the Renin Inhibitors[4-7]

Adverse Events	Single Entity Agents	Combination Products
	Aliskiren	Aliskiren and HCTZ
Cardiovascular		
Hypotension	<1	<1
Peripheral edema	✔	✔
Central Nervous System		
Dizziness	>1	2
Fatigue	>1	>1
Headache	>1	>1
Restlessness	-	✔
Seizure	✔	✔
Vertigo	1	1
Dermatologic		
Erythema multiforme	-	✔
Exfoliative dermatitis	-	✔
Photosensitivity	-	✔
Rash	1	1
Stevens-Johnson syndrome	-	✔
Toxic epidermal necrolysis	-	✔
Urticaria	-	✔
Endocrine and Metabolic		
Gout	<1	<1
Gastrointestinal		
Abdominal pain	✔	✔
Cramping	-	✔
Diarrhea	2	2
Dyspepsia	✔	✔
Gastric irritation	-	✔
Gastroesophageal reflux	✔	✔
Genitourinary		
Glycosuria	-	✔
Hematologic		
Agranulocytosis	-	✔
ALT increased	-	1
Anemia	✔	-
Aplastic anemia	-	✔
Hematocrit decreased	✔	✔
Hemoglobin decreased	✔	✔
Hemolytic anemia	-	✔
Leukopenia	-	✔
Thrombocytopenia	-	✔
Laboratory Test Abnormalities		
Alanine aminotransaminase increased	-	1
Blood urea nitrogen increased	7	12
Creatine kinase increased	1	-
Hyperglycemia	-	✔
Hyperkalemia	1	1

Adverse Events	Single Entity Agents	Combination Products
	Aliskiren	Aliskiren and HCTZ
Hypokalemia	-	2
Serum creatinine increased	7	1
Uric acid increased	<1	<1
Musculoskeletal		
Arthralgia	-	1
Asthenia	-	1
Back pain	>1	>1
Muscle cramps	-	-
Muscle spasm	-	✔
Myositis	<1	-
Rhabdomyolysis	<1	-
Weakness	-	✔
Renal		
Interstitial nephritis	-	✔
Renal dysfunction	-	✔
Renal failure	-	✔
Renal stones	<1	<1
Respiratory		
Cough	1	1
Influenza	-	2
Nasopharyngitis	✔	>1
Respiratory distress	-	✔
Sinusitis	-	-
Upper respiratory infection	>1	>1
Other		
Allergic reaction	-	-
Angioedema	✔	✔
Blurred vision	-	✔
Edema (face, hands, or whole body)	<1	<1
Fever	-	✔
Jaundice	-	✔
Necrotizing angiitis	-	✔
Pancreatitis	-	✔
Periorbital edema	✔	✔
Purpura	-	✔
Xanthopsia	-	✔

✔ Percent not specified.
- Event not reported.

Table 7. Boxed Warning for Aliskiren Products[4]

WARNING
When pregnancy is detected, discontinue aliskiren as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.

VII. Dosing and Administration

The usual dosing regimens for the renin inhibitors are listed in Table 8.

Table 8. Usual Dosing Regimens for the Renin Inhibitors[4-7]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Aliskiren	Hypertension: Tablet: initial, 150 mg once daily; maintenance, titrate as needed; maximum, 300 mg/day	Hypertension in pediatric patients 6 to 17 years of age: Tablet: 20 to 50 kg, initial, 75 mg once daily; maximum, 150 mg daily; ≥50 kg, follow adult dosing	Tablet: 150 mg 300 mg
Combination Products			
Aliskiren and HCTZ	Hypertension: Tablet: initial, 150-12.5 mg once daily; maximum, 300-25 mg/day	Safety and efficacy in children have not been established.	Tablet: 150-12.5 mg 150-25 mg 300-12.5 mg 300-25 mg

HCTZ=hydrochlorothiazide

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the renin inhibitors are summarized in Table 9.

Table 9. Comparative Clinical Trials with the Renin Inhibitors

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cardiovascular Risk Reduction				
Parving et al.[18] (2012) ALTITUDE Aliskiren vs placebo Both in addition to standard treatment	DB, PC, RCT Patients ≥35 years of age with type 2 diabetes and evidence of microalbuminuria, macroalbuminuria, or cardiovascular disease	N=8,561 Median of 32.9 months	Primary: Composite of death from cardiovascular causes or the first occurrence of cardiac arrest with resuscitation; nonfatal MI; nonfatal stroke; unplanned hospitalization for HF; end-stage renal disease, death attributable to kidney failure, or the need for renal-replacement therapy with no dialysis or transplantation available or initiated; or a serum creatinine value that was at least double the baseline value and that exceeded the upper limit of the normal range Secondary: Composite of cardiovascular	The independent data and safety monitoring committee recommended termination of the study medication, on the basis of their assessment that the excess risk of adverse events in the aliskiren group could not be offset by a reduction in major cardiovascular and renal events. Primary: The primary outcome occurred in 783 participants in the aliskiren group (18.3%) and 732 in the placebo group (17.1%). The hazard ratio for this outcome in the aliskiren group as compared with the placebo group was 1.08 (95% CI, 0.98 to 1.20; P=0.12). Secondary: The secondary cardiovascular composite outcome occurred in 590 participants in the aliskiren group (13.8%) and 539 in the placebo group (12.6%); the HR in the aliskiren group was 1.11 (95% CI, 0.99 to 1.25; P=0.09). The secondary renal composite outcome occurred in 257 participants in the aliskiren group (6.0%) and 251 in the placebo group (5.9%); the HR in the aliskiren group was 1.03 (95% CI, 0.87 to 1.23; P=0.74). The number of deaths from any cause did not differ significantly between the study groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			components and of renal components of the primary composite end point	
McMurray et al.[19] (2016) ATMOSPHERE Enalapril 5 or 10 mg BID vs aliskiren 150 mg QD vs combination of aliskiren 150 mg QD and enalapril 5 or 10 mg BID	DB, DD, RCT Patients with CHF (NYHA class II to IV) and EF ≤35% receiving stable doses of an ACE inhibitor (equivalent to at least 10 mg of enalapril daily) and of a β-blocker at the time of enrollment	N=7,016 Median of 36.6 months	Primary: Composite of death from cardiovascular causes or hospitalization for heart failure Secondary: Change from baseline to 12 months in the Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score	Primary: Overall, the primary outcome occurred in 770 patients (32.9%) in the combination-therapy group (11.7 events per 100 person-years), in 791 patients (33.8%) in the aliskiren group (12.1 events per 100 person-years), and in 808 patients (34.6%) in the enalapril group (12.4 events per 100 person-years). The hazard ratio in the combination-therapy group, as compared with the enalapril group, was 0.93 (95% CI, 0.85 to 1.03; P=0.17); the hazard ratio in the aliskiren group, as compared with the enalapril group, was 0.99 (95% CI, 0.90 to 1.10; P=0.91 for superiority). Although the noninferiority margin of 1.104 was met with the use of the 95% confidence interval, the one-sided P value of 0.0184 did not fulfill the prespecified requirement of a P value of 0.0123 or less. A sensitivity analysis that included only patients who received the assigned trial regimen gave consistent results, as did an analysis in which data that were collected after regulatory censoring were included. Secondary: There were no significant between-group differences in the secondary outcome. The exploratory composite renal outcome (the composite of death from renal causes, end-stage renal disease, or doubling of the serum creatinine level) occurred significantly more frequently in the combination-therapy group than in the enalapril group.
Hypertension				
Tocci et al.[20] (abstract) 2012 Aliskiren 150 to 300 mg/day	MC, OL, OS, PRO Patient with HTN not adequately controlled on ≥2 other antihypertensive agents	N=1,186 12 months	Primary: Efficacy, safety Secondary: Not reported	Primary: SBP and DBP was 141.1/82.4, 134.9/79.8, and 133.6/78.9 mmHg at one, six and 12 month follow-up visits, respectively (P<0.0001 vs baseline for all comparisons). These effects were consistent in all predefined subgroups, including those with left ventricular hypertrophy, renal disease, diabetes mellitus, CAD, or cerebrovascular disease. Reduced levels of microalbuminuria were reported, without affecting other renal and electrolyte parameters.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Oh et al.[21] (2007) Aliskiren 150, 300, or 600 mg QD vs placebo	DB, MC, PC, PG, RCT Men and women ≥18 years (mean age 53 years) with mild-to-moderate essential HTN (DBP ≥95 and <110 mm Hg)	N=672 8 weeks	Primary: Change in mean sitting DBP Secondary: Change in mean sitting SBP, 24-hour ABPM, proportion achieving a successful treatment response (DBP <90 mm Hg or ≥10 mm Hg pressure reduction from baseline) or blood pressure control (<140/90 mm Hg), plasma renin activity and concentration, safety and tolerability	Primary: All three doses investigated provided significantly greater reductions in mean sitting DBP from baseline compared to placebo (P<0.0001 for all). The mean sitting DBP reductions were 10.3 mm Hg with 150 mg, 11.1 mm Hg with 300 mg and 12.5 mm Hg with 600 mg compared to 4.9 mm Hg with placebo. Secondary: All three doses provided significantly greater reductions in mean sitting SBP from baseline compared to placebo (P<0.0001 for all). The mean sitting SBP reductions were 13.0 mm Hg with 150 mg, 14.7 mm Hg with 300 mg and 15.8 mm Hg with 600 mg compared to 3.8 mm Hg with placebo. Reduction in the 24-hour ABPM was significantly greater in all doses of aliskiren compared to placebo (n=216; P<0.0001 for all). Reductions in mean ambulatory DBP and SBP were consistent across the 24-hour dosing interval with all aliskiren doses. The proportion of patients achieving a successful treatment response was 59.3% with aliskiren 150 mg, 63.3% with 300 mg and 69.3% with 600 mg compared to 36.2% with placebo (P<0.0001 for all). The proportion of patients achieving blood pressure control was 35.9% with 150 mg, 41.6% with 300 mg and 46.4% with 600 mg compared to 20.3% with placebo (P<0.0001 for all). Plasma renin activity decreased 79.5% with 150 mg, 81.1% with 300 mg and 75.0% with 600 mg compared to an increase of 19.5% with placebo. Aliskiren resulted in dose-dependent increases from baseline in renin concentrations (51.5%, 101.6%, and 228.5% for 150, 300 and 600 mg, respectively). Renin concentrations were almost unchanged with placebo.
Kushiro et al.[22] (2006)	DB, MC, PC, PG, RCT	N=455 8 weeks	Primary: Change in mean sitting DBP	Primary: All three aliskiren doses provided significantly greater reductions in mean sitting DBP from baseline compared to placebo. The placebo-corrected

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Aliskiren 75, 150, or 300 mg QD vs placebo	Japanese men and women between the ages of 20 and 80 years with essential HTN (mean sitting DBP of ≥90 mm Hg and <110 mm Hg during the run-in period and ≥95 mm Hg and <110 mm Hg at baseline)		Secondary: Change in mean trough sitting SBP, proportion of patients responding to treatment (mean sitting DBP <90 mm Hg and/or ≥10 mm Hg decrease in mean sitting DBP from baseline), dose-response relationship, safety	reductions in mean sitting DBP were 4.0 mm Hg with 75 mg aliskiren, 4.5 mm Hg with 150 mg and 7.5 mm Hg with 300 mg (P<0.0005 for all). Secondary: The mean sitting SBP reductions were significantly lower with all aliskiren doses when compared to placebo. The placebo-corrected reductions in mean sitting SBP were 5.7 mm Hg with 75 mg aliskiren, 5.9 mm Hg with 150 mg and 11.2 mm Hg with 300 mg (P<0.001 for all). The proportion of responders at study end point was 47.8% with aliskiren 75 mg, 48.2% with 150 mg and 63.7% with 300 mg compared to 27.8% with placebo (P<0.005 for all). Dose-response analysis showed that the relationship between reductions in mean sitting DBP and SBP and aliskiren dose was almost linear. However, further analyses revealed that a pattern of similar reductions with aliskiren 75 and 150 mg and greater reductions with aliskiren 300 mg was a better fit for both mean sitting DBP and SBP. The incidence of drug-related adverse events was comparable between aliskiren (53 to 55%) and placebo (50%). There was no evidence of a dose-dependent increase in the incidence of all-causality adverse events at the aliskiren doses evaluated in this study.
Musini et al.[23] (2009) Aliskiren (variable doses) vs placebo	MA Patients ≥18 years of age with mild to moderate essential HTN (defined as mean sitting DBP ≤95 mm Hg and ≤110 mm Hg at baseline)	N=3,694 (6 trials) 8 weeks	Primary: Changes in dose-related SBP and DBP Secondary: Variability of blood pressure, pulse pressure, heart rate, withdrawals due to adverse effects, and rates of specific adverse effects	Primary: Aliskiren monotherapy was more effective than placebo in lowering mean sitting SBP. The additional magnitude of blood pressure lowering minus the placebo effect: aliskiren 75 mg vs placebo -2.94 (95% CI, -4.56 to -1.31); aliskiren 150 mg vs placebo -5.45 (95% CI, -6.46 to -4.43); aliskiren 300 mg vs placebo -8.66 (95% CI, -9.68 to 7.64); aliskiren 600 mg vs placebo -11.36 (95% CI, -13.53 to -9.19). Aliskiren monotherapy was more effective than placebo in lowering mean sitting DBP. The additional magnitude of blood pressure lowering minus the placebo effect: aliskiren 75 mg vs placebo -2.29 (95% CI, -3.31 to -1.26); aliskiren 150 mg vs placebo -3.00 (95% CI, -3.65 to -2.34); aliskiren 300 mg vs placebo -4.97 (95% CI, -5.62 to -4.31); aliskiren 600 mg vs placebo -6.57 (95% CI, -7.92 to -5.23).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: No trials reported on pulse pressure at baseline or end point. Two trials recorded baseline heart rate, but no data were provided at week eight. There were no significant differences in withdrawals between placebo and aliskiren at any dose. The relative risk for aliskiren 75 mg vs placebo was 0.97 (95% CI, 0.49 to 1.89); for aliskiren 150 mg vs placebo was 1.01 (95% CI, 0.61 to 1.69); for aliskiren 300 mg vs placebo was 0.91 (95% CI, 0.57 to 1.47) and for aliskiren 600 mg vs placebo was 0.63 (9% CI, 0.21 to 1.89). One trial reported on the incidence of dry cough: placebo (1.1%); aliskiren 75 mg (1.1%); aliskiren 150 mg (2.8%); aliskiren 300 mg (0.6%). No trials reported angioedema. The blood pressure lowering efficacy of aliskiren 150 mg vs 75 mg, as well as aliskiren 600 mg vs 300 mg was not significantly different. Aliskiren 300 mg significantly lowered both SBP and DBP as compared to 150 mg (SBP: -2.97; 95% CI, -3.99 to -1.95; DBP: -1.66; 95% CI, -2.32 to -1.0).
Braun-Dullaeus et al.[24] (2012) Aliskiren 150 mg QD, up titrated to 300 mg QD vs placebo All patients received amlodipine 5 mg/day, up titrated	DB, MC, RCT Patients with HTN (mean sitting SBP ≥160 to <200 mm Hg	N=485 8 weeks	Primary: Change in baseline mean sitting SBP and DBP, blood pressure control rate (<140/90 mm Hg) Secondary: Safety	Primary: After eight weeks, add-on treatment with aliskiren resulted in significantly greater reductions in mean sitting SBP and DBP compared to placebo (-37.7/-16.1 vs -30.6/-12.3 mm Hg; P<0.0001). After eight weeks, significantly more patients receiving aliskiren add-on therapy achieved blood pressure control compared to placebo (67.0 vs 49.1%; P=0.0001). Secondary: The overall incidence of adverse events was similar between both treatments. The most commonly reported adverse event was peripheral edema, with a higher incidence occurring in patients receiving placebo (18.3 vs 14.4%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
up to 10 mg/day.				
Weinberger et al.[25] (abstract) 2012 AACESS Aliskiren 150 mg/day, up titrated to 300 mg/day vs placebo All patients were receiving amlodipine 5 mg/day, up titrated to 10 mg/day	DB, RCT African American patients with stage 2 HTN (mean sitting SBP 160 to 199 mm Hg) with obesity or metabolic syndrome	N=489 8 weeks	Primary: Change in baseline mean sitting SBP Secondary: Not reported	Primary: LSM reductions in mean sitting SBP were significantly higher with add-on aliskiren compared to placebo in both obese (-33.7 vs -27.9 mm Hg; P<0.001) and metabolic syndrome patients (-36.4 vs -28.5 mm Hg; P< 0.001). Secondary: Not reported
Teo et al.[26] (2014) APOLLO Aliskiren 300 mg daily vs placebo and amlodipine 5 mg daily or	DB, PC, RCT Patients ≥65 years with SBP between 130 and 159 mm Hg with either CVD or one additional CV risk factor	N=11,000 5 years Study was terminated by sponsor after 1759 subjects were randomized and followed for 0.6 year due to non-scientific reasons without any knowledge	Primary: Original endpoints (risks of the composite of CV death, non-fatal MI, non-fatal stroke, and clinically significant heart failure) could not be assessed, so tolerability and effects on BP lowering were reported Secondary: Not reported	Primary: Postrandomization, aliskiren reduced adjusted mean SBP by 3.5 (SE [standard error] 0.5) mmHg, (P<0.001), and DBP by 1.7 (SE 0.3) mmHg (P<0.001) compared with placebo (first co-primary outcome), HCTZ or amlodipine by 6.8 (SE 0.5) mmHg, (P<0.001) for SBP and 3.3 (SE 0.3) mmHg (P<0.001) for DBP. The reduction in SBP in the double therapy compared with double placebo (second co-primary outcome) was 10.3 (SE 0.8) mmHg (P<0.001) for SBP, and 5.0 (SE 0.5) mmHg, P<0.001 in mean DBP. There were few serious adverse events, both during run-in and after randomization, with no excess associated with any treatment group. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
HCTZ 25 mg daily		of blinded trial data and despite objections of the Steering Committee		
Schmieder et al.[27] (2009) Aliskiren 150 to 300 mg QD (with optional addition of amlodipine 5 to 10 mg QD) vs HCTZ 12.5 to 25 mg QD (with optional addition of amlodipine 5 to 10 mg QD) vs placebo for 6 weeks, then randomized to either aliskiren 300 mg QD or HCTZ 25 mg QD	AC, DB, RCT Adults with essential HTN	N=1,124 12 months	Primary: Safety and change in mean sitting DBP Secondary: Change in mean sitting SBP	Primary: The proportion of patients who experienced adverse events during the six week placebo-controlled period was similar in the aliskiren monotherapy, HCTZ monotherapy, and placebo groups (26.4, 24.5, and 28.5%, respectively). During the 52 week double-blind treatment period, adverse events were reported by a similar proportion of patients receiving the aliskiren and hydrochlorothiazide regimens. Most adverse events were mild or moderate in intensity. At week 26, the aliskiren regimen provided significantly greater reductions from baseline in DBP compared to HCTZ (-14.2 and -13.0 mm Hg, respectively; P<0.05). The greater reduction in DBP with the aliskiren regimen compared to the HCTZ regimen was maintained at week 52 (-16.0 and -15.0 mm Hg, respectively; P<0.05). Secondary: At week 26, the aliskiren regimen provided significantly greater reductions from baseline in SBP compared to HCTZ (-20.3 and -18.6 mm Hg, respectively; P<0.05). Reductions in SBP at week 52 were not inferior to those of HCTZ (-22.1 and -21.2 mm Hg, respectively; P<0.0001 for non-inferiority).
Schmieder et al.[28] (2009) Aliskiren 150 mg QD, followed by 300 mg QD after 3	Subgroup analysis of obese patients in Schmieder et al.[25] Patients 18 years of age and older with	N=1,124 52 weeks	Primary: Mean sitting DBP Secondary: Mean sitting SBP at week 26, mean	Primary: The LSM DBP and SBP reductions at week 12 were significantly greater with aliskiren compared to HCTZ (P<0.0001 and P=0.001 respectively). Secondary: At week 52, aliskiren resulted in significantly greater mean sitting DBP

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
weeks vs HCTZ 12.5 mg QD, followed by 25 mg QD after 3 weeks vs placebo, followed by aliskiren 300 mg QD or HCTZ 25 mg QD after 6 weeks	essential HTN, a mean sitting DBP ≥90 and <110 mm Hg; at randomization, patients had to have a mean sitting DBP ≥95 and <110 mm Hg and show a difference of ≤10 mm Hg since the previous visit		sitting DBP and SBP at week 52, proportion of patients with response to treatment, blood pressure control at weeks 26 and 52, and safety	reductions compared to HCTZ (P<0.001). Blood pressure response rates were significantly greater with aliskiren compared to HCTZ at both week 12 and week 52 (P<0.05). Significantly more obese patients achieved blood pressure control with aliskiren compared to HCTZ at week 12 (P=0.0013). Blood pressure control rates were similar between groups at week 52 (P value not reported).
Littlejohn et al.[29] (2009) Aliskiren 150 to 300 mg and amlodipine 5 to 10 mg QD HCTZ may be added if additional blood pressure control was required.	OL, MC Patients ≥18 years of age with essential HTN (mean sitting DBP ≥90 mm Hg and <110 mm Hg)	N=556 12 months	Primary: Safety and tolerability Secondary: Blood pressure-lowering efficacy	Primary: Long-term treatment with aliskiren and amlodipine was generally well tolerated. In total, 76.3% of patients reported at least one adverse event. The majority were mild or moderate in severity and transient. The most frequently reported adverse events were peripheral edema, upper respiratory tract infection, headache, and bronchitis. Peripheral edema was reported in 20.5% of patients who received aliskiren and amlodipine and in 14.0% of patients who received aliskiren and amlodipine and HCTZ. Edema was reported as mild in 59.5%, moderate in 33.3% and severe in 7.1% of patients. Secondary: At week two, treatment with aliskiren/amlodipine led to a mean reduction in blood pressure of 13.5/8.3 mm Hg. At week 10, there was a mean reduction in blood pressure of 23.5/15.1 mm Hg. Blood pressure reductions were sustained from week 10 until the end of the study. At week 54, aliskiren and amlodipine decreased mean blood pressure from 153.5/97.6 mm Hg at baseline to 129.4/82.2 mm Hg (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The BP control rate was 74.3% with aliskiren/amlodipine at week 54.
Drummond et al.[30] (2007) Aliskiren and amlodipine 150-5 mg QD (fixed-dose combination product) vs amlodipine 5 mg QD vs amlodipine 10 mg QD Patients not responding to amlodipine 5 mg QD at the end of 4 week single-blind run-in period received combination therapy, continuation of amlodipine 5 mg QD or titration to amlodipine 10 mg QD.	AC, DB, MC, PG, RCT Patients 18 years of age and older with mild to moderate HTN	N=545 6 weeks	Primary: Change in DBP at 6 weeks Secondary: SBP, comparison of SBP and DBP reductions between combination therapy group and amlodipine 10 mg group, proportion of patients responding to treatment, and proportion of patients achieving blood pressure control	Primary: DBP reduction was significantly greater in the combination therapy group compared to those in the amlodipine 5 mg group (P<0.0001). Secondary: SBP reduction was significantly greater in the combination therapy group compared to those in the amlodipine 5 mg group (P<0.0001). No significant differences were observed in DBP or SBP reduction between the combination therapy group and the amlodipine 10 mg group (P=0.6167 and P=0.2666 respectively). The proportion of patients responding to treatment was significantly higher in the combination therapy group compared to the amlodipine 5 mg group (P<0.0001). No significant difference was observed between the combination therapy group and the amlodipine 10 mg group (P value not reported). The proportion of patients achieving blood pressure control was significantly higher in the combination therapy group compared to the amlodipine 5 mg group (P<0.0001). No significant difference was observed between the combination therapy group and the amlodipine 10 mg group (P=0.5229).
Villamil et al.[31] (2007)	DB, MC, PC, RCT	N=2,776	Primary: Change in mean	Primary: Aliskiren monotherapy significantly reduced mean sitting DBP (P=0.0002).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Aliskiren 75 to 300 mg QD vs HCTZ 6.25 to 25 mg QD vs aliskiren and HCTZ (every dose combination except aliskiren 300 mg and HCTZ 6.25 mg) QD vs placebo	Men and women ≥18 years with mild-to-moderate essential HTN	8 weeks	sitting DBP Secondary: Change in mean sitting SBP, dose-response efficacy for all treatment groups, proportion achieving a successful response (DBP <90 mm Hg or ≥10 mm Hg), proportion achieving blood pressure control (<140/90 mm Hg), plasma renin activity, renin concentrations, safety	Only the aliskiren 150 and 300 mg doses were more effective than placebo (P=0.09 for aliskiren 75 mg). HCTZ monotherapy significantly reduced DBP from baseline (P<0.01 for all vs placebo). All combinations were more effective than placebo (P<0.0001) with reductions in DBP ranging from 10.4 to 14.3 mm Hg. Most combination regimens were more effective than monotherapy with the individual components (exceptions were aliskiren 150 mg and HCTZ 6.25 mg vs monotherapy, and aliskiren 75 mg and HCTZ 12.5 mg vs HCTZ monotherapy). Secondary: After eight weeks of therapy, aliskiren 150 and 300 mg regimens (both P<0.0001) were more effective than placebo in lowering mean sitting SBP, but the 75 mg dose was not (P=0.151). Combination therapy was consistently more effective in reducing SBP than monotherapy with the individual components, with the exception of aliskiren 75 mg plus HCTZ 12.5 vs HCTZ monotherapy. Reductions in SBP with combination therapy ranged from 14.3 to 21.2 mm Hg. Blood pressure reductions were related to the doses of both aliskiren and HCTZ. Responder rates were significantly higher with aliskiren 300 mg (63.9%; P=0.0005), HCTZ 12.5 and 25 mg (60.6 and 59.0%, respectively; both P<0.02) and all combination doses (58.4 to 80.6%; all P<0.05) than placebo (45.8%). Responder rates for all combinations of aliskiren and HCTZ 25 mg, and aliskiren 300 mg and HCTZ 12.5 mg were higher than both monotherapies (P<0.05), while aliskiren 75 mg and HCTZ 12.5 mg and aliskiren 150 mg and HCTZ 12.5 mg were more effective than their respective aliskiren monotherapies (P<0.05). In the aliskiren and HCTZ monotherapy groups, only aliskiren 300 mg led to statistically significantly greater control rates than placebo (46.7 vs 28.1%; P=0.0001). Control rates for all combinations, with the exception of aliskiren 75 mg and HCTZ 6.25 mg, were higher than placebo (all P<0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was a trend towards improved control rates with combination therapy (37.4 to 59.5%) compared to aliskiren monotherapy (29.0 to 46.7%) or HCTZ monotherapy (32.5 to 37.8%). Combinations utilizing the higher doses of one or both drugs (aliskiren 75 to 300 mg with HCTZ 25 mg or aliskiren 150 to 300 mg with HCTZ 12.5 mg) yielded control rates that were significantly higher than monotherapy with either component. While all doses of aliskiren decreased plasma renin activity and all doses of HCTZ increased plasma renin activity, combination therapy resulted in decreased plasma renin activity of 46.1 to 63.5%. Renin concentrations increased in all monotherapy and combination regimens with the exception of HCTZ 6.25 and 12.5 mg. All active treatments were well tolerated with 37.3 to 39.2% of patients experiencing adverse events with aliskiren monotherapy, 38.7 to 42.0% with HCTZ monotherapy, 34.6 to 45.3% with aliskiren and HCTZ, and 44% with placebo. Hypokalemia (serum potassium <3.5 mmol/L) occurred with the highest frequency with HCTZ 12.5 and 25 mg (3.9 and 5.2%, respectively). When administered in combination with aliskiren, the frequency of hypokalemia was 0.7 to 2.0% with HCTZ 12.5 mg and 2.2% to 3.4% with HCTZ 25 mg.
Maddury et al.[32] (2013) aliskiren vs aliskiren + hydrochlorothiazide (HCT) single-pill combination	MC, OBS, OL, PRO Patients ≥18 years of age with a diagnosis of hypertension for which aliskiren or aliskiren HTC therapy had been prescribed by the treating physician	N=4,826 26 ± 8 weeks	Primary: Proportion of patients who achieved therapeutic goal, defined as a target BP <140/90 mmHg Secondary: Absolute change from baseline to end of study in mean sitting SBP (msSBP) and mean sitting DBP (msDBP), and the	Primary: The proportion of patients who reached the defined therapeutic BP goal at week 26 was 49.2% overall, 49.5% for aliskiren, and 48.3% for aliskiren HCT. Secondary: At week 26, the proportion of aliskiren-treated patients achieving the predefined response for SBP and DBP was 83.6 and 84.4%, respectively; the corresponding BP response rates in patients receiving aliskiren HCT were 84.4 and 86.5%. Treatment with aliskiren and aliskiren HCT was also associated with significant reductions from baseline to the end of study in msSBP and msDBP (P<0.001 vs baseline for both treatments). Adverse effects occurred in a total of 101 (2.1%) patients. The most common AEs included headache, onset of diabetes mellitus, abdominal discomfort, and dizziness.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			proportion of patients achieving a BP response, safety	
Fukutomi et al.[33] (2014) Aliskiren 150 mg/ amlodipine 5 mg group (AL/AM), after 8 weeks aliskiren dose was doubled to 300 mg for another 8 weeks vs high-dose amlodipine 10 mg (AM) group	MC, OL, RCT Hypertensive patients who were untreated or being treated with 5mg amlodipine During a 4-week run-in period, untreated patients started 5 mg amlodipine monotherapy and treated patients continued their medication. At the end of the run-in period, patients with BP ≥140mm Hg and/or diastolic BP (DBP) ≥90mm Hg were considered eligible for the study	N=87 4-week run-in plus 16 weeks of treatment	Primary: Brachial flow-mediated vasodilation (FMD) and nitroglycerin-mediated vasodilation (NMD) Secondary: Not reported	Primary: FMD significantly improved in the AL/AM group but significantly decreased in the AM group. At the end of the study, FMD was significantly higher in the AL/AM group than in the AM group (3.7±1.9% vs. 2.3±1.1%; P<0.001). NMD did not change after the treatment period in either group. Secondary: Not reported
Jordan et al.[34] (2007) Aliskiren 150 to 300 mg QD, added to existing HCTZ therapy (single entity products)	DB, DD, MC, PG, RCT Obese men and women (BMI ≥30 kg/m^2) ≥18 years with essential HTN (mean sitting DBP 95 to 109 mm Hg	N=489 12 weeks	Primary: Change in mean sitting DBP with aliskiren 300 mg plus HCTZ vs HCTZ alone at 8 weeks Secondary:	Primary: Aliskiren 300 mg added to HCTZ 25 mg significantly reduced mean sitting DBP compared to HCTZ alone at week eight (mean difference, -4.0; P<0.0001). Secondary: Aliskiren 300 mg added to HCTZ caused numerically larger reductions in mean sitting DBP and SBP compared to amlodipine 10 mg plus HCTZ and irbesartan 300 mg plus HCTZ at week eight, but there were no statistically

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs amlodipine 5 to 10 mg QD, added to existing HCTZ therapy (single entity products) vs irbesartan 150 to 300 mg QD, added to existing HCTZ therapy (single entity products) vs HCTZ 25 mg QD (existing therapy)	and SBP <180 mm Hg) who had not responded to 4 weeks of treatment with HCTZ 25 mg		Comparisons of mean sitting DBP and SBP with aliskiren plus HCTZ vs the other treatment groups, percentage of responders (mean sitting DBP <90 mm Hg or ≥10 mm Hg reduction from baseline), proportion of patients achieving blood pressure control (mean sitting blood pressure <140/90 mm Hg), plasma renin activity, safety and tolerability	significant differences between treatment groups (P>0.05). Responder rates were significantly higher with aliskiren plus HCTZ than HCTZ alone at week eight (P=0.0193) and week 12 (P=0.004) but comparable to responder rates observed with amlodipine plus HCTZ (P>0.05) and irbesartan plus HCTZ (P>0.05). The proportion of patients achieving blood pressure control was significantly higher with aliskiren plus HCTZ than HCTZ alone at week eight (P=0.0005) and week 12 (P=0.0001) but not statistically different than amlodipine plus HCTZ (P>0.05) and irbesartan plus HCTZ (P>0.05). Plasma renin activity significantly increased (P<0.05) during four weeks of HCTZ monotherapy. Combination with aliskiren neutralized this increase and led to an overall significant reduction in plasma renin activity compared to pretreatment baseline (P<0.05) whereas amlodipine and irbesartan led to further significant increases (P<0.05). All of the study treatments were generally well tolerated. Amlodipine plus HCTZ (45.2%) was associated with a higher incidence of adverse events than the other treatment groups (36.1 to 39.3%), largely due to a higher rate of peripheral edema (11.1 vs 0.8 to 1.6%).
Nickenig et al.[35] (2008) Aliskiren and HCTZ 300-25 mg QD (fixed-dose combination) vs aliskiren and HCTZ 300-12.5 mg QD (fixed-dose combination)	DB, MC, RCT Patients with HTN and an inadequate response to aliskiren (mean sitting DBP >90 and ≤110 mm Hg following 4 weeks of aliskiren 300 mg)	N=880 8 weeks	Primary: Changes in mean sitting SBP and DBP, rates of blood pressure control (<140/90 mm Hg) Secondary: Not reported	Primary: Treatment with aliskiren and HCTZ 300-25 mg and 300-12.5 mg led to significantly greater reductions in mean sitting SBP/DBP from baseline (15.9/11.0 mm Hg and 13.5/10.5 mm Hg, respectively) compared to aliskiren 300 mg (8.0/7.4 mm Hg; both P<0.001). Rates of blood pressure control were significantly higher with aliskiren and HCTZ 300-25 mg (60.2%) and 300-12.5 mg (57.9%) compared to aliskiren 300 mg (40.9%; both P<0.001). Patients treated with aliskiren and HCTZ or aliskiren monotherapy demonstrated similar tolerability. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs aliskiren 300 mg QD (existing therapy)				
Blumenstein et al.[36] (2009) Aliskiren and HCTZ 300-25 mg QD (fixed-dose combination product) vs aliskiren and HCTZ 150-25 mg QD (fixed-dose combination product) vs HCTZ 25 mg (existing therapy)	DB, MC, RCT Patients with HTN and an inadequate response to HCTZ (mean sitting DBP >90 and ≤110 mm Hg following 4 weeks of HCTZ 25 mg)	N=722 8 weeks	Primary: Changes in mean sitting SBP/DBP, proportion of patients achieving blood pressure control (mean sitting blood pressure <140/90 mm Hg), and blood pressure response rates (msDBP <90 mm Hg or a ≥10 mm Hg decrease from baseline) Secondary: Not reported	Primary: The mean reductions in mean sitting SBP/DBP from baseline with aliskiren and HCTZ 300-25 and 150-25 mg were significantly greater compared to those achieved with HCTZ monotherapy (P<0.001 for all). Rates of blood pressure control were significantly higher with aliskiren and HCTZ 300-25 and 150-25 mg compared to HCTZ monotherapy (P<0.001 for both). Aliskiren and HCTZ 300-25 mg provided significantly greater reductions in mean sitting SBP/DBP and rates of blood pressure control compared to aliskiren and HCTZ 150-25 mg dose (P<0.05 for all). Blood pressure response rates were significantly higher with aliskiren and HCTZ 300-25mg (78.5%) and aliskiren and HCTZ 150-25 mg (67.4%) compared to HCTZ monotherapy (47.1%; P<0.001 for both comparisons). All treatments were generally well-tolerated and the proportion of patients experiencing adverse events was similar across treatment groups. The majority of adverse events were mild and transient. Adverse events reported in >2% of patients were nasopharyngitis, dizziness, back pain, and vertigo. The proportion of patients with serum potassium <3.5 mmol/L was lower with aliskiren and HCTZ (1.3 to 2.2%) compared to HCTZ monotherapy (3.4%). Hyperkalemia (serum potassium >5.5 mmol/L) was observed in only one patient receiving aliskiren and HCTZ and two patients in the HCTZ monotherapy group. No patient had increases in serum creatinine above the pre-specified clinically significant threshold. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Lacourciere et al.[37] (2012) Aliskiren and amlodipine and HCTZ 150-5-12.5 mg /day (fixed-dose combination product), up titrated to double the initial dose vs aliskiren and amlodipine 150-5 mg/day (fixed-dose combination product) , up titrated to double the initial dose vs aliskiren and HCTZ 150-12.5 mg/day (fixed-dose combination product) , up titrated to double the initial dose vs amlodipine and HCTZ 5-12.5 mg/day (fixed-	DB, RCT Patients ≥18 years of age with moderate to severe HTN	N=1,191 8 weeks	Primary: Change in baseline mean sitting SBP and DBP, blood pressure control rate (<140/90 mm Hg) Secondary: Safety	Primary: Treatment with aliskiren and amlodipine and HCTZ resulted in significant LSM reductions in mean sitting SBP/DBP (week 4: -30.7/-15.9 mm Hg; week 8: -37.9/-20.6 mm Hg) compared to any combination therapy (P<0.001 for all). Significant reductions with triple therapy were observed as early as two weeks compared to dual therapies (P<0.05). Significantly more patients receiving aliskiren and amlodipine and HCTZ achieved blood pressure control compared to dual therapies with moderate to severe (62.3%) and severe (57.5%) HTN. Secondary: The majority of adverse events were mild or moderate in nature. The overall incidence of events was comparable among treatments (36.2 vs 33.4 vs 32.3 vs 33.6%). Peripheral edema was the most commonly reported adverse event.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dose combination product)* , up titrated to double the initial dose				
Ferdinand et al.[38] (abstract) (2012) Aliskiren and amlodipine and HCTZ 300-10-25 mg /day (fixed-dose combination product) vs aliskiren and amlodipine 150-5 mg/day (fixed-dose combination product)	Subgroup analysis Patients with HTN and any of the following: diabetes, cardiometabolic syndrome, obesity, or black patients	N=not reported 8 weeks	Primary: Change in baseline mean sitting SBP Secondary: Not reported	Primary: LSM reductions in mean sitting SBP, across all subgroups ranged from 35 to 37 mm Hg with aliskiren and amlodipine and HCTZ compared to 28 to 30 mm Hg with aliskiren and amlodipine (P<0.01). Secondary: Not reported
Gradman et al.[39] (2005) Aliskiren 150 to 600 mg QD vs irbesartan 150 mg QD vs placebo	DB, MC, PC, PG, RCT Men and women, age 18 years or older, with mild-to-moderate essential HTN (mean sitting DBP ≥95 mm Hg and <110 mm Hg)	N=652 8 weeks	Primary: Change in mean sitting DBP and SBP Secondary: Proportion of patients achieving blood pressure control (<140/90 mm Hg), safety	Primary: Decreases in mean sitting DBP at eight weeks were significantly greater with all doses of aliskiren compared to placebo (P<0.001). The least-squares mean reductions in trough DBP for aliskiren 150, 300, and 600 mg were 9.3, 11.8, and 11.5 mm Hg, respectively, vs 6.3 mm Hg for placebo. Decreases in mean sitting SBP at eight weeks were significantly greater with all doses of aliskiren compared to placebo (P<0.001). The least-squares mean reductions in trough SBP for aliskiren 150, 300, and 600 mg were 11.4, 15.8, and 15.7 mm Hg, respectively, vs 5.3 mm Hg for placebo. The antihypertensive effect of aliskiren 150 mg was comparable to irbesartan 150 mg with reductions of 8.9 and 12.5 mm Hg for mean sitting DBP and SBP, respectively. Aliskiren 300 and 600 mg produced significantly greater mean sitting DBP reductions than irbesartan 150 mg

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(P<0.05). While the reductions in mean sitting SBP were greater with aliskiren 300 and 600 mg than irbesartan 150 mg, these differences were not statistically significant). Secondary: The percentage of patients achieving blood pressure control was significantly greater with all doses of aliskiren (37.8%-150 mg, 50.0%-300 mg, 45.7%-600 mg) and irbesartan (33.8%) compared to placebo (20.8%; P<0.05). More patients on aliskiren 300 and 600 mg achieved blood pressure control compared to irbesartan (P<0.05). Drug-related adverse events for both aliskiren and irbesartan were comparable to placebo and the most commonly reported adverse events were headache, dizziness, and diarrhea. The number of patients discontinuing therapy was similar in all groups.
O'Brien et al.[40] (2007) Aliskiren 150 mg QD for 3 weeks, then HCTZ 25 mg QD was added for an additional 3 weeks (if ABPM remained ≥135/85 mm Hg) vs irbesartan 150 mg QD for 3 weeks, then aliskiren 75 mg QD added for 3 weeks, then aliskiren 150 mg QD added for 3 weeks	3 OL studies Men and women 18 to 80 years with ambulatory SBP ≥140 and ≤180 mm Hg without treatment	N=67 6 to 9 weeks	Primary: Change in daytime systolic ABPM with combination therapy compared to monotherapy Secondary: Change in daytime diastolic ABPM, nighttime systolic and diastolic ABPM, daytime and nighttime heart rates, plasma renin activity	Primary: Aliskiren coadministered with HCTZ (P=0.0007) or ramipril (P=0.03) led to significantly greater reductions in daytime systolic ABPM compared to monotherapy. There was a trend for a reduction in daytime systolic ABPM with the addition of aliskiren to irbesartan; however, this trend was not statistically significant. Secondary: Aliskiren plus HCTZ significantly lowered daytime diastolic ABPM compared to aliskiren monotherapy (P=0.0006). Changes in nighttime systolic and diastolic ABPM followed similar trends but did not achieve statistical significance (P=0.06 and P=0.09, respectively). No changes in heart rate were observed with either aliskiren regimen. Aliskiren added to irbesartan did not significantly change diastolic ABPM compared to irbesartan monotherapy; however, nighttime systolic and diastolic ABPM were significantly reduced (P<0.05 for all). No changes in heart rate were observed with either irbesartan regimen. Mean diastolic ABPM was significantly decreased with the addition of aliskiren 150 mg (P<0.05) but not aliskiren 75 mg to ramipril monotherapy. Both aliskiren doses significantly decreased nighttime systolic and diastolic

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vs ramipril 5 mg QD for 3 weeks, then aliskiren 75 mg QD added for 3 weeks, then aliskiren 150 mg QD added for 3 weeks				ABPM (P<0.05 for all). No changes in heart rate were observed with either ramipril regimen. Aliskiren alone significantly inhibited plasma renin activity by 65% (P<0.0001), while ramipril and irbesartan monotherapy increased renin activity by 90 and 175%, respectively. When aliskiren was coadministered with HCTZ, ramipril or irbesartan, plasma renin activity remained similar to baseline levels or decreased.
Strasser et al.[41] (2007) Aliskiren 150 to 300 mg QD vs lisinopril 20 to 40 mg QD HCTZ may be added if additional blood pressure control was required.	AC, DB, DD, MC, PG, RCT Men and women with uncomplicated severe HTN (mean sitting DBP 105 to 119 mm Hg)	N=183 8 weeks	Primary: Safety Secondary: Change in mean sitting DBP and SBP, percentage of responders	Primary: Both active treatments were well tolerated with an incidence of adverse events of 32.8% for aliskiren and 29.3% for lisinopril. The proportion of patients discontinuing treatment due to adverse events was 3.2% for aliskiren and 3.4% for lisinopril. The most frequently reported adverse events in both groups were headache, nasopharyngitis and dizziness. Secondary: Aliskiren showed similar reductions from baseline to lisinopril in mean sitting DBP (-18.5 vs -20.1 mm Hg) and SBP (-20.0 and -22.3 mm Hg). Responder rates were 81.5% with aliskiren and 87.9% with lisinopril. Approximately half of patients required the addition of HCTZ to achieve blood pressure control (53.6% for aliskiren and 44.8% for lisinopril).
Stanton et al.[42] (2003) Aliskiren 37.5 to 300 mg QD vs losartan 100 mg QD	AC, DB, MC, RCT Men and women 21 to 70 years of age with mild-to-moderate HTN (SBP ≥140 mm Hg)	N=226 4 weeks	Primary: Change in daytime ambulatory SBP Secondary: Changes in clinic SBP and DBP, plasma renin activity, plasma aliskiren levels,	Primary: A dose-dependent reduction in daytime ambulatory SBP was observed with increasing aliskiren doses (with mean changes of -0.40 mm Hg with aliskiren 37.5 mg, -5.3 mm Hg with aliskiren 75 mg, -8.0 mm Hg with aliskiren 150 mg, and -11 mm Hg with aliskiren 300 mg; P=0.0002). The change in daytime SBP with losartan 100 mg (-10.9 mm Hg) was significantly different than aliskiren 37.5 mg, but not the other higher aliskiren dosages). Secondary:

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			adverse events	Clinic SBP and DBP, both in the sitting and standing positions, decreased with aliskiren in a dose-dependent manner, whereas heart rate was unaltered. The decreases in clinic blood pressures were similar for losartan 100 mg and aliskiren 150 and 300 mg. Dose-dependent reductions in plasma renin activity were also observed (median change -55, -60, -77, and -83% with 37.5, 75, 150, and 300 mg aliskiren, respectively; P=0.0008). By contrast, plasma renin activity increased by 110% with losartan 100 mg. Rate of adverse events was 22% with aliskiren 37.5 mg, 35% with aliskiren 75 mg, 25% with aliskiren 150 mg, 23% with aliskiren 300 mg, and 32% with losartan 100 mg. There was no increase in the number of adverse events when increasing the dose of aliskiren.
Uresin et al.[43] (2007) Aliskiren 150 to 300 mg QD vs ramipril 5 to 10 mg QD vs aliskiren 150 to 300 mg and ramipril 5 to 10 mg QD	DB, MC, RCT Patients ≥18 years of age with type 1 or type 2 diabetes mellitus and stage 1 to 2 HTN (mean sitting DBP) >95 and <110 mm Hg)	N=837 8 weeks	Primary: Change in mean sitting DBP Secondary: Change in mean sitting SBP, proportion of patients with a successful response to treatment (trough mean sitting DBP <90 mm Hg and/or ≥10 mm Hg reduction from baseline), rates of blood pressure control (blood pressure <130/80 mm Hg), changes from baseline in 24-hour ABPM measurements, and	Primary: Aliskiren monotherapy, ramipril monotherapy, and aliskiren and ramipril combination therapy lowered mean sitting DBP by 11.3, 10.7, and 12.8 mm Hg, respectively. Treatment with aliskiren and ramipril combination therapy produced significantly greater reductions from baseline in mean sitting DBP compared to either aliskiren monotherapy (P=0.043) or ramipril monotherapy (P=0.004). Aliskiren 300 mg was statistically non-inferior (P=0.0002) to ramipril 10 mg for the change in mean sitting DBP. Secondary: Aliskiren monotherapy, ramipril monotherapy, and aliskiren and ramipril combination therapy lowered mean sitting SBP by 14.7, 12.0, and 16.6 mm Hg, respectively. Treatment with aliskiren and ramipril combination therapy produced significantly greater reductions from baseline in mean sitting SBP compared to ramipril monotherapy (P<0.0001), but not aliskiren monotherapy (P=0.088). Aliskiren monotherapy was statistically superior to ramipril for the change in mean sitting SBP (P=0.021). The proportion of patients with a successful response to therapy was similar for aliskiren and ramipril combination therapy (74.1%) and aliskiren monotherapy (73.1%). The responder rates in both groups were significantly higher (P<0.05) compared to ramipril monotherapy (65.8%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			changes in biomarkers (plasma renin concentration, plasma renin activity, aldosterone)	Rates of blood pressure control with aliskiren and ramipril combination pressure (13.1%) were not significantly different compared to aliskiren monotherapy (8.2%) or ramipril monotherapy (8.4%). All treatments significantly lowered mean 24-hour ambulatory blood pressure. Aliskiren and ramipril combination therapy was significantly more effective compared to ramipril monotherapy in lowering 24-hour mean ambulatory DBP (P=0.034). There was no significant difference in 24-hour ambulatory SBP compared to ramipril monotherapy. Aliskiren significantly reduced plasma renin activity from baseline as monotherapy (by 66%, P<0.0001) or in combination with ramipril (by 48%, P<0.0001).
Duprez et al.[44] (2010) AGELESS Aliskiren 150 to 300 mg QD vs ramipril 5 to 10 mg QD The addition of HCTZ was allowed at week 12 and amlodipine was allowed at week 22 in patients not achieving adequate blood pressure control.	AC, DB, MC, RCT Patients ≥65 years of age with essential HTN (mean sitting SBP ≥140 and <180 mm Hg and mean sitting DBP <110mm Hg)	N=901 36 weeks	Primary: Change in mean seated SBP at week 12 Secondary: Change in mean sitting SBP at week 36, change in mean sitting DBP at week 12 and week 36, percentage of patients who achieved blood pressure control (mean sitting SBP/DBP <140/90 mm Hg in non-diabetic patients and <130/80 mm Hg in diabetic patients) at week 12 and week 36, percentage of	Primary: At week 12, aliskiren lowered mean sitting SBP by 14 mm Hg and ramipril decreased mean sitting SBP by 11.6 mm Hg (difference, -2.3 mm Hg; 95% CI, -4.3 to -0.3). Aliskiren monotherapy showed statistically non-inferior (P<0.001) and statistically superior (P=0.02) reductions in mean sitting SBP compared to ramipril monotherapy. Secondary: At week 22, aliskiren decreased mean sitting SBP by 19.6 mm Hg and ramipril decreased mean sitting SBP by 17 mm Hg (difference, -2.4 mm Hg; 95% CI, -4.5 to -0.3; P=0.03). At week 36, aliskiren decreased mean sitting SBP by 20 mm Hg and ramipril decreased mean sitting SBP by 18.1 mm Hg (difference, -1.9 mm Hg; 95% CI, -4.0 to 0.2; P=0.07). At week 12, aliskiren decreased mean sitting DBP by 5.1 mm Hg and ramipril decreased mean sitting DBP by 3.6 mm Hg (difference, -1.5 mm Hg; 95% CI, -2.6 to -0.5; P<0.01). At week 22, aliskiren decreased mean sitting DBP by 8.2 mm Hg and ramipril decreased mean sitting DBP by 7.3 mm Hg (difference, -0.8 mm Hg; 95% CI, -2.0 to 0.3; P=0.14).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			patients who required add-on therapy	At week 36, aliskiren decreased mean sitting DBP by 8.2 mm Hg and ramipril decreased mean sitting DBP by 7.0 mm Hg (difference, -1.2 mm Hg; 95% CI, -2.3 to -0.1; P=0.03). The percentage of patients achieving blood pressure control was significantly greater with aliskiren (42%) compared to ramipril (33%) at week 12 (P<0.01). At week 22, a significantly greater proportion of patients achieved blood pressure control with aliskiren (62%) compared to ramipril (50%; P<0.001). At week 36, similar blood pressure control rates were achieved with aliskiren (59%) and ramipril (51%; P=0.01). By week 36, a significantly greater percentage of patients receiving ramipril compared to aliskiren required additional HCTZ (56 vs 46%; P<0.01). By week 36, a greater percentage of patients receiving ramipril (16%) compared to aliskiren (12%) required add-on therapy with both HCTZ and amlodipine (P=0.048). More patients receiving aliskiren were receiving monotherapy (42%) than patients receiving ramipril (29%) at week 36.
Anderson et al.[45] (2008) Aliskiren 150 to 300 mg QD vs ramipril 5 to 10 mg QD The addition of HCTZ was allowed in patients not achieving adequate blood	AC, DB, MC, PC, RCT Men and women ≥18 years with essential HTN (mean sitting DBP 90 to 109 mm Hg)	N=842 26 weeks	Primary: Change in mean sitting DBP at week 26 Secondary: Change in mean sitting SBP at week 26, change in mean sitting SBP and DBP at week 6 and 12 (comparing aliskiren and ramipril monotherapy), proportion	Primary: Reductions in mean sitting DBP at week 26 were significantly greater with aliskiren-based therapies (-13.2 mm Hg) compared to ramipril-based therapies (-12.0 mm Hg; P=0.0250). Secondary: Reductions in mean sitting SBP at week 26 were significantly greater with aliskiren-based therapies (-17.9 mm Hg) compared to ramipril-based therapies (-15.2 mm Hg; P=0.0036). Mean changes in sitting SBP were significantly greater with aliskiren (-12.9 and -14.0 mm Hg, respectively) compared to ramipril (-10.5 and -11.3, respectively) at weeks six and 12 (P=0.0041 and P=0.0027, respectively). Mean changes in sitting DBP were not significantly greater with aliskiren

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
pressure control. The study did not specifically analyze the effects of HCTZ on either treatment regimen.			achieving blood pressure control (<140/90 mm Hg), proportion achieving SBP control (<140 mm Hg), safety	(-10.5 and -11.3 mm Hg, respectively) compared to ramipril (-9.5 and -9.7, respectively) at week six, but were significantly greater at week 12 (P=0.0689 and P=0.0056, respectively). The proportion of patients achieving overall blood pressure control (<140/90 mm Hg) was significantly higher with aliskiren-based therapy (61.4%) compared to ramipril-based therapy (53.1%; P=0.0205) at week 26. Also, the proportion of patients achieving SBP control (<140 mm Hg) was significantly higher with aliskiren-based therapy (72.5%) compared to ramipril-based therapy (64.1%; P=0.0075) at week 26. The majority of adverse events reported during the active treatment period were mild or moderate in intensity and transient. Most events occurred at a similar incidence in the two groups with the exception of cough which was considered treatment-related in 5.5% of patients receiving ramipril vs 2.1% of patients receiving aliskiren.
Oparil et al.[46] (2007) Aliskiren 150 to 300 mg QD vs valsartan 160 to 320 mg QD vs aliskiren 150 to 300 mg and valsartan 160 toe 320 mg QD (single entity products) vs	DB, MC, PC, RCT Men and women aged 18 years or over with stage 1-2 essential HTN (mean sitting DBP 95 to 109 mm Hg and 8-hr ambulatory DBP ≥90 mm Hg)	N=1,797 8 weeks	Primary: Change in mean sitting DBP Secondary: Change in mean sitting SBP, proportion of patients achieving a successful response to treatment (mean sitting DBP <90 mm Hg and/or ≥10 mm Hg reduction from baseline) or achieving blood pressure control (mean sitting SBP/DBP <140/90 mm Hg), change in 24-hr ABPM,	Primary: The combination of aliskiren 300 mg and valsartan 320 mg lowered mean sitting DBP from baseline by 12.2 mm Hg, significantly more than either monotherapy with aliskiren 300 mg (-9.0 mm Hg; P<0.0001), valsartan 320 mg (-9.7 mm Hg; P<0.0001) or with placebo (-4.1 mm Hg; P<0.0001). Monotherapy with aliskiren or valsartan provided significantly greater reductions in mean sitting DBP than did placebo at week 8 (P<0.0001 for all). Secondary: The combination of aliskiren 300 mg and valsartan 320 mg lowered mean sitting SBP from baseline by 17.2 mm Hg, significantly more than either monotherapy with aliskiren 300 mg (-13.0 mm Hg; P<0.0001), valsartan 320 mg (-12.8 mm Hg; P<0.0001), or with placebo (-4.6 mm Hg; P<0.0001). Monotherapy with aliskiren or valsartan provided significantly greater reductions in mean sitting SBP than did placebo at week eight end point (all P<0.0001). The proportion of patients achieving a successful response to treatment at week eight was significantly higher with the combination of aliskiren and valsartan (66%) than with aliskiren alone (53%; P=0.0003) or valsartan

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placebo			change in biomarkers, safety	alone (55%; P=0.0010). All active treatments were associated with significantly greater responder rates than placebo (30%; P<0.0001 for all). The proportion of patients achieving blood pressure control was significantly greater in the combination group (49%) than in the aliskiren (37%; P=0.0005) or valsartan (34%; P<0.0001) monotherapy groups. All active treatments were associated with significantly greater control rates than placebo (16%; P<0.0001 for all). The combination of aliskiren and valsartan was significantly more effective in lowering mean 24-hr ambulatory SBP and DBP than was either agent alone (P<0.0001 for all). The greater reductions in ambulatory blood pressure with aliskiren plus valsartan were maintained throughout the entire 24-hour dosing interval. Aliskiren and valsartan (P<0.0001) and monotherapy with aliskiren (P<0.0001) or valsartan (P=0.0002) provided significant increases in plasma renin concentrations versus placebo. Increases in plasma renin concentrations were significantly greater for the combination than aliskiren (P=0.0014) or valsartan (P<0.0001) monotherapy. Valsartan monotherapy produced significantly greater increases in plasma renin activity than placebo (160 vs 18%; P=0.0003). By contrast, aliskiren alone significantly reduced plasma renin activity by 73% (P<0.0001 vs placebo), while the combination of aliskiren plus valsartan led to a reduction in plasma renin activity of 44% (P<0.0001 vs placebo). The combination of aliskiren and valsartan (-31%; P<0.0001) and valsartan monotherapy (-25%; P=0.0007) provided significantly greater reductions in plasma aldosterone concentration than did placebo (7%), while aliskiren monotherapy had no significant effect (-5.9%; P=0.1059). Rates of adverse events and laboratory abnormalities were similar in all groups.
Yarows et al.[47] (2008)	Post-hoc analysis of patients with stage 2 HTN from Oparil et	N=1,797 8 weeks	Primary: Change in mean sitting DBP	Primary: In patients with stage 2 HTN, significantly greater reductions in DBP were demonstrated in the aliskiren and valsartan 300-320 mg group compared to

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Aliskiren 150 mg QD for 4 weeks, followed by 300 mg QD for 4 weeks vs valsartan 160 mg QD for 4 weeks, followed by 320 mg QD for 4 weeks vs aliskiren and valsartan 150-160 mg QD for 4 weeks, followed by 300-320 mg QD for 4 weeks (fixed-dose combination products) vs placebo	al.[48] Men and women ≥18 years of age with stage 1 to 2 essential HTN (mean sitting DBP 95 to 109 mm Hg and 8-hour ambulatory DBP ≥90 mm Hg)		Secondary: Change in mean sitting SBP, proportion of patients achieving a successful response to treatment (mean sitting DBP <90 mm Hg and/or ≥10 mm Hg reduction from baseline) or achieving blood pressure control (mean sitting SBP/DBP <140/90 mm Hg)	either higher-dose monotherapy group (P<0.05) and placebo (P<0.0001). Secondary: In patients with stage 2 HTN, significantly greater reductions in SBP were demonstrated in the aliskiren and valsartan 300-320 mg group compared to either higher-dose monotherapy group (P<0.05) and placebo (P<0.0001). DBP and SBP reductions in both monotherapy groups were significantly greater compared to placebo (P<0.0001). The proportion of patients with stage 2 HTN achieving blood pressure control at week eight was significantly greater in the aliskiren and valsartan 300-320 mg group compared to both monotherapy groups and placebo (P≤0.044). Blood pressure control rates in the aliskiren group were significantly greater than placebo (P<0.001). No significant difference was observed between the valsartan monotherapy and placebo groups.
Bakris et al.[48] (2013) VIvID Therapy with aliskiren/valsartan 150/160 mg titrated to 300/320	AC, DB, RCT Hypertensive adults with type 2 diabetes and stage 1 or 2 chronic kidney disease (CKD)	N=1143 8 weeks	Primary: ABP Secondary: Safety	Primary: Both treatments produced significant reductions from baseline to week 8 in all ABPM measures (P<0.0001). The addition of aliskiren to valsartan was associated with an incremental benefit of 4.0 mm Hg of lowering in 24-hour mean ambulatory (ma)SBP and 2.4 mm Hg of lowering in 24-hour maDBP (both P<0.001). Secondary:

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mg vs valsartan monotherapy 160 mg titrated to 320 mg				Adverse events were experienced by 202 participants (35.2%) in the combination aliskiren/valsartan group and by 182 participants (32.2%) in the valsartan group.
Pool et al.[49] (2007) Aliskiren 75 to 300 mg QD vs valsartan 80 to 320 mg vs aliskiren 75 to 300 mg and valsartan 80 to 320 mg vs valsartan and HCTZ 160-12.5 mg QD (fixed-dose combination) vs placebo	DB, MC, PC, PG, RCT Men and women ≥18 years with mild-to-moderate essential HTN (mean sitting DBP ≥95 mm Hg after a 3- to 4-week single-blind placebo run-in period)	N=1,123 8 weeks	Primary: Change in mean sitting DBP Secondary: Change in mean sitting SBP, safety	Primary: Aliskiren 300 mg significantly (P<0.0001) lowered mean sitting DBP compared to placebo. Reductions in mean sitting DBP for aliskiren 75 and 150 mg compared to placebo failed to reach statistical significance (P=0.052 and P=0.051, respectively). Secondary: Aliskiren 300 mg significantly (P<0.0001) lowered mean sitting SBP compared to placebo. A statistically significant linear dose relationship was observed for the effect of aliskiren (75 to 300 mg) on mean sitting DBP (P=0.0002) and mean sitting SBP (P=0.0005). The effects of aliskiren monotherapy on mean sitting DBP and SBP across the 75 to 300 mg dose range were similar to the effects of valsartan 80 to 320 mg. Coadministration of aliskiren and valsartan produced a greater antihypertensive effect than either drug alone. Reductions in mean sitting DBP and SBP obtained with aliskiren 150 mg plus valsartan 160 mg and aliskiren 300 mg plus valsartan 320 mg were not significantly different from those observed with valsartan 160 mg plus HCTZ 12.5 mg. Responder rates were significantly greater than placebo for all 3 aliskiren monotherapy groups and for all aliskiren plus valsartan combinations. The proportion of responders with aliskiren 75 mg plus valsartan 80 mg was significantly greater than either component monotherapy (P<0.05). There was no significant difference between the proportion of responders to aliskiren 150 mg plus valsartan 160 mg or aliskiren 300 mg plus valsartan 320 mg compared to valsartan 160 mg plus HCTZ 12.5 mg.

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				Control rates were higher with aliskiren 300 mg compared to placebo and with valsartan 160 mg plus HCTZ 12.5 mg compared to aliskiren 150 mg plus valsartan 160 mg, but there were no significant differences between aliskiren plus valsartan combinations and the respective monotherapies. Aliskiren and valsartan were generally well tolerated either as monotherapy or in combination. The overall incidence of adverse events and rate of discontinuations because of adverse events were similar to placebo in all active treatment groups.
Geiger et al.[50] (2009) Aliskiren 150 to 300 mg QD, added to existing HCTZ therapy vs valsartan 160 to 320 mg QD, added to existing HCTZ therapy vs aliskiren 150 to 300 mg and valsartan 160 to 320 mg QD, added to existing HCTZ therapy vs HCTZ 25 mg QD	AC, DB, RCT Patients ≥18 years of age with mild to moderate essential HTN who were taking HCTZ for 4 weeks with a DBP ≥95 mm Hg	N=641 8 weeks	Primary: Change in DBP at week 8 Secondary: Change SBP at week 8, change in DBP and SBP at week 4, proportion of patients achieving blood pressure control (SBP/DBP <140/90 mm Hg), change in plasma renin activity, plasma renin concentration	Primary: After eight weeks of therapy, the triple therapy showed significantly greater reductions in SBP and DBP compared to the other groups. The additional SBP and DBP reductions were 7 and 5 mm Hg, respectively compared to aliskiren and HCTZ (P<0.0001), 3 and 2 mm Hg compared to valsartan and HCTZ (P<0.01), and 15 and 10 mm Hg compared to HCTZ monotherapy (P<0.001). Aliskiren and HCTZ and valsartan and HCTZ combination therapies were more effective compared to HCTZ monotherapy. Valsartan and HCTZ was more effective than aliskiren and HCTZ. SBP and DBP were reduced by 15 and 11 mm Hg, respectively in the aliskiren and HCTZ group. SBP and DBP were reduced by 18 and 14 mm Hg, respectively, in the valsartan and HCTZ group. Secondary: Blood pressure control rate was significantly higher with triple therapy compared to aliskiren and HCTZ (40.9%, P<0.001), valsartan and HCTZ (48.7%, P<0.001), and HCTZ monotherapy (20.5%, P<0.001). At week four, a significantly greater blood pressure control rate was observed for the triple therapy group at lower doses (150-160-25 mg) compared to the respective doses of the other groups: aliskiren and valsartan and HCTZ (300-320-25 mg) group (56%) compared to aliskiren and HCTZ (36.6%, P<0.05), valsartan and HCTZ (42.2%, P<0.05), and HCTZ monotherapy (19.9%, P<0.01). At week eight, plasma renin concentration was unchanged in the HCTZ

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				group, but was significantly increased in other groups. A significant decrease in plasma renin activity from baseline was observed in the aliskiren and HCTZ group (P<0.001) and a significant increase was observed in the valsartan and HCTZ (P<0.001). In the HCTZ and triple therapy groups, there was no change in plasma renin activity (both P>0.75).
Dietz et al.[51] (2008) Aliskiren 150 to 300 mg QD vs atenolol 50 to 100 mg QD vs aliskiren 150 to 300 mg and atenolol 50 to 100 mg QD	RCT, DB, MC Patients ≥18 years of age with HTN (mean sitting DBP ≥95 and <110 mm Hg)	N=694 12 weeks	Primary: Changes in mean sitting SBP and mean sitting DBP, rates of blood pressure control (<140/90 mm Hg), pulse pressure and pulse rate, plasma renin concentration, plasma renin activity Secondary: Not reported	Primary: Treatment with aliskiren and atenolol combination therapy led to a significantly greater reduction in mean sitting SBP by 17.3 mm Hg compared to aliskiren monotherapy (difference, -2.9 mm Hg; P=0.039) or atenolol monotherapy (difference, -3.0 mm Hg; P=0.034). There was no difference between mean sitting SBP reductions with aliskiren and atenolol monotherapy (difference, -0.1 mm Hg; P=0.954). Treatment with aliskiren and atenolol combination therapy led to a significantly greater reduction in mean sitting DBP by 14.1 mm Hg compared to aliskiren monotherapy (difference, -2.9 mm Hg; P<0.001), but not atenolol monotherapy (difference, -0.5 mm Hg; P=0.545). Reductions in mean sitting DBP with atenolol were larger compared to those observed with aliskiren (difference, 2.4 mm Hg; P=0.003). Rates of blood pressure control were higher with aliskiren and atenolol combination therapy (51.3%) compared to aliskiren monotherapy (36.1%, P<0.001) or atenolol monotherapy (42.2%, P=0.009). There was no significant difference in blood pressure control rates between aliskiren and atenolol monotherapy (P=0.388). Mean pulse pressure was reduced by 3.0 mm Hg with aliskiren and atenolol combination therapy and aliskiren monotherapy. Atenolol monotherapy did not affect pulse pressure. Aliskiren monotherapy did not affect pulse rate. Significant mean reductions in pulse rate of >10 bpm were observed with atenolol monotherapy and the aliskiren and atenolol combination (P<0.001 vs aliskiren monotherapy for both). Aliskiren monotherapy increased plasma renin concentration by 241% and aliskiren/atenolol increased plasma renin concentration by 85% (P=0.010 vs aliskiren). Atenolol monotherapy decreased plasma renin concentration by 24% (P<0.001 vs aliskiren and aliskiren/atenolol). Aliskiren, atenolol

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				and aliskiren/atenolol reduced plasma renin activity by 65, 52, and 61%, respectively. Secondary: Not reported
Stanton et al.[52] (2010) Aliskiren 300 mg QD vs irbesartan, losartan, valsartan, ramipril, HCTZ, placebo	MA Adults with mild to moderate essential HTN	N=4,877 (8 trials) 4 to 12 weeks	Primary: Paradoxical blood pressure rises, as well as the percentage of patients with SBP increases (>10 or >20 mm Hg) or DBP increases (>5 or >10 mm Hg) from baseline Secondary: Not reported	Primary: There were no significant differences among the pooled aliskiren, irbesartan, losartan, valsartan, ramipril, and HCTZ groups in the incidence of SBP increases >10 mm Hg (P=0.30) and >20 mm Hg (P=0.28) or DBP increases >5 mm Hg (P=0.65) and >10 mm Hg (P=0.5). Increases in SBP and DBP occurred significantly more frequently in the pooled placebo group than the aliskiren group (P<0.001). Secondary: Not reported
Wiysonge et al.[53] (2007) Other antihypertensive therapies (i.e., placebo, diuretics, calcium channel blockers, or renin-angiotensin system inhibitors) vs β-blockers (atenolol, metoprolol, oxprenolol*, or	MA 13 RCTs evaluating patients ≥18 years of age with HTN	N=91,561 Duration varied	Primary: All-cause mortality Secondary: Stroke, CHD, cardiovascular death, total cardiovascular disease, adverse reactions	Primary: There was not a significant difference observed in all-cause mortality between β-blocker therapy and placebo (RR, 0.99; 95% CI, 0.88 to 1.11; P value not reported), diuretics (RR, 1.04; 95% CI, 0.91 to 1.19; P value not reported) or renin-angiotensin system inhibitors (RR, 1.10; 95% CI, 0.98 to 1.24; P value not reported). There was a significantly higher rate in all-cause mortality with β-blocker therapy compared to calcium channel blockers (RR, 1.07; 95% CI, 1.00 to 1.14; P=0.04). Secondary: There was a significant decrease in stroke observed with β-blocker therapy compared to placebo (RR, 0.80; 95% CI, 0.66 to 0.96). Also there was a significant increase in stroke with β-blocker therapy compared to calcium channel blockers (RR, 1.24; 95% CI, 1.11 to 1.40) and renin-angiotensin system inhibitors (RR, 1.30; 95% CI, 1.11 to 1.53), but there was no difference observed compared to diuretics (RR, 1.17; 95% CI, 0.65 to 2.09).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
propranolol)				CHD risk was not significantly different between β-blocker therapy and placebo (RR, 0.93; 95% CI, 0.81 to 1.07]), diuretics (RR, 1.12; 95% CI, 0.82 to 1.54), calcium channel blockers (RR, 1.05; 95% CI, 0.96 to 1.15) or renin-angiotensin system inhibitors (RR, 0.90; 95% CI, 0.76 to 1.06). The risk of total cardiovascular disease was lower with β-blocker therapy compared to placebo (RR, 0.88; 95% CI, 0.79 to 0.97). The effect of β-blocker therapy on cardiovascular disease was significantly worse than that of calcium channel blockers (RR, 1.18; 95% CI, 1.08 to 1.29), but was not significantly different from that of diuretics (RR, 1.13; 95% CI, 0.99 to 1.28) or renin-angiotensin system inhibitors (RR, 1.00; 95% CI, 0.72 to 1.3). There was a significantly higher rate of discontinuation due to side effects with β-blocker therapy compared to diuretics (RR, 1.86; 95% CI, 1.39 to 2.50) and renin-angiotensin system inhibitors (RR, 1.41; 95% CI, 1.29 to 1.54), but there was no significant difference compared to calcium channel blockers (RR, 1.20; 95% CI, 0.71 to 2.04). Actual side effects were not reported.
Baguet et al.[54] (2007) Antihypertensive drugs (enalapril, ramipril, trandolapril, candesartan, irbesartan, losartan, olmesartan, telmisartan, valsartan, HCTZ, indapamide SR*, atenolol, amlodipine, lercanidipine*, manidipine*,	MA Patients greater than 18 years of age with mild or moderate essential HTN (SBP 140 to 179 mm Hg and/or DBP 90 to 109 mm Hg)	N=10,818 8 to 12 weeks	Primary: Weighted average reductions in SBP and DBP Secondary: Not reported	Primary: Data did not reflect outcomes from direct, head-to-head comparative trials or formal comparisons between drugs. Diuretics (-19.2 mm Hg; 95% CI, -20.3 to -18.0), calcium channel blockers (-16.4 mm Hg; 95% CI, -17.0 to -15.8) and ACE inhibitors (-15.6 mm Hg; 95% CI, -17.6 to -13.6) produced the greatest reductions in SBP from baseline (P values not reported). The magnitude of DBP reductions were generally similar among all drug classes; however, the greatest reductions in DBP from baseline were observed with the β-blocker, atenolol (-11.4 mm Hg; 95% CI, -12.0 to -10.9), calcium channel blockers (-11.4 mm Hg; 95% CI, -11.8 to -11.1) and diuretics (-11.1 mm Hg; 95% CI, -11.7 to -10.5) (P values were not reported). The weighted average reduction of SBP and DBP for each drug class were as follows: Diuretics: -19.2 (95% CI, -20.3 to -18.0) and -11.1 mm Hg (95% CI, -11.7 to -10.5), respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
enalapril, ramipril, trandolapril, and aliskiren) Drugs were used as monotherapy, either at a fixed daily dosage or in increasing dosages. Although cicletanine*, furosemide and spironolactone were considered for inclusion, none of the trials relating to these agents satisfied all inclusion criteria.				β-blockers: -14.8 (95% CI, -15.9 to -13.7) and -11.4 mm Hg (95% CI, -12.0 to -10.9), respectively. Calcium channel blockers: -16.4 (95% CI, -17.0 to -15.8) and -11.4 mm Hg (95% CI, -11.8 to -11.1), respectively. ACE inhibitors: -15.6 (95% CI, -17.6 to -13.6) and -10.8 mm Hg (95% CI, -11.9 to -9.7), respectively. ARBs: -13.2 (95% CI, -13.6 to -12.9) and -10.3 mm Hg (95% CI, -10.5 to -10.1), respectively. Renin inhibitor: -13.5 (95% CI, -14.2 to -12.9) and -11.3 mm Hg (95% CI, -11.7 to -10.9), respectively. Secondary: Not reported
Diabetes/Diabetic Nephropathy/Renal Dysfunction				
Persson et al.[55] (2009) Aliskiren 300 mg QD vs irbesartan 300 mg QD vs aliskiren 300 mg QD and irbesartan	DB, RCT, XO Adults with type 2 diabetes, HTN, and albuminuria	N=26 Four 2-month treatment periods	Primary: Albuminuria (urinary albumin excretion rate) Secondary: 24-hour blood pressure, GFR	Primary: Treatment with aliskiren led to a significant reduction in albuminuria by 48% compared to placebo (P<0.001). Treatment with irbesartan led to a significant reduction in albuminuria by 58% compared to placebo (P<0.001). There was no significant difference in albuminuria between aliskiren and irbesartan (P value not reported). The combination of aliskiren and irbesartan significantly reduced albuminuria by 71% compared to placebo (P<0.001), which was also significantly better than with monotherapy (P<0.001 for aliskiren and P=0.028 for irbesartan). Secondary: SBP and DBP 24-hr blood pressure were reduced by 3 and 4 mm Hg, respectively by aliskiren (P value not significant and P=0.009, respectively), 12 and 5 mm Hg, respectively by irbesartan (P<0.001 and P=0.002, respectively), and 10 and 6 mm Hg, respectively with the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
300 mg QD vs placebo				combination (P=0.001 and P <0.001, respectively) compared to placebo. There was no significant change in 24-hr blood pressure with irbesartan compared to combination therapy. GFR was significantly reduced 4.6 mL/min/1.73 m^2 with aliskiren (P=0.037), 8.0 mL/min/1.73 m^2 with irbesartan (P<0.001), and 11.7 mL/min/1.73 m^2 with the combination (P<0.001) compared to placebo.
Parving et al.[56] (2008) AVOID Aliskiren 150 mg QD for 3 months, followed by 300 mg QD for 3 months vs placebo Study medications were added to losartan 100 mg and other pre-existing antihypertensive treatments.	DB, MC, PC, RCT Hypertensive patients who were 18 to 85 years of age who had type 2 diabetes and nephropathy	N=599 6 months	Primary: Reduction in albumin:creatinine ratio at 6 months Secondary: Blood pressure reductions, adverse events	Primary: Treatment with aliskiren 300 mg/day as compared to placebo reduced the mean urinary albumin:creatinine ratio by 20% (95% CI, 9 to 30; P<0.001), with a reduction of 50% or more in 24.7% of the patients who received aliskiren as compared to 12.5% of those who received placebo (P<0.001). Secondary: A small difference in blood pressure was seen between the treatment groups by the end of the study period with SBP and DBP pressures 2 and 1 mm Hg lower, respectively, in the aliskiren group (P=0.07 and P=0.08, respectively). The total numbers of adverse and serious adverse events were similar in the groups.
Miscellaneous				
Solomon et al.[57] (2009) ALLAY Aliskiren 300 mg QD vs	AC, RCT Adults with HTN and increased left ventricular wall thickness	N=465 9 months	Primary: Change in left ventricular mass Secondary: Not reported	Primary: There were reductions in left ventricular mass from baseline in all treatment groups, with 4.9 g/m^2 (5.4%), 4.8 g/m^2 (4.7%), and 5.8 g/m^2 (6.4%) reductions in the aliskiren, losartan, and combination arms, respectively (P<0.0001 for all treatment groups). The reduction in left ventricular mass in the combination group was not significantly different from that with losartan alone (P=0.52).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
losartan 100 mg QD vs aliskiren 300 mg and losartan 100 mg QD				The difference in left ventricular mass regression between the aliskiren and losartan arms was within the prespecified non-inferiority margin, suggesting that aliskiren was as effective as losartan in reducing left ventricular hypertrophy (P<0.0001 for non-inferiority). Secondary: Not reported
McMurray et al.[58] (2008) ALOFT Aliskiren 150 mg QD vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with NYHA class II to IV heart failure, current or past history of NTH, and plasma brain natriuretic peptide concentration >100 pg/mL who had been treated with an ACE inhibitor (or angiotensin receptor blocker) and β-blocker	N=302 3 months	Primary: N-terminal pro-brain natriuretic peptide, brain natriuretic peptide, aldosterone, signs and symptoms of heart failure echocardiographic measures of cardiac size and ventricular function, blood pressure, heart rate variability, quality of life, neurohumoral and inflammatory biomarkers, and glycemic measures Secondary: Not reported	Primary: Plasma N-terminal pro- brain natriuretic peptide increased by 762 pg/mL with placebo and decreased by 244 pg/mL with aliskiren (P=0.0106). Brain natriuretic peptide decreased by a mean of 12.2 pg/mL in the placebo group and by 61.0 pg/mL in the aliskiren group (P=0.0160). Plasma aldosterone did not differ between groups. Urinary aldosterone decreased with aliskiren by 9.24 nmol/day and by 6.96 nmol/day with placebo (P=0.0150). Plasma renin activity decreased 5.71 $ng \cdot mL^{-1} \cdot h^{-1}$ with aliskiren compared to a decrease of 0.97 $ng \cdot mL^{-1} \cdot h^{-1}$ with placebo (P<0.0001). There was no difference between treatments for change in signs or symptoms of heart failure, echocardiographic measurements of wall thickness, chamber volumes, or LVEF. The mean decrease in seated systolic blood pressure was 1.7 mm Hg in the placebo group and 4.1 mm Hg in the aliskiren group (P=0.2257). The mean decrease in seated diastolic blood pressure was 0.2 mm Hg in the placebo group and 2.9 mm Hg in the aliskiren group (P=0.0599). The mean increase in seated heart rate was 0.2 bpm in the placebo group and 1.1 bpm in the aliskiren group (P=0.6774). Mean standing systolic blood pressure decreased by 1.7 mm Hg in the placebo group and by 3.5 mm Hg in the aliskiren group (P=0.497). The mean standing diastolic blood pressure increased by 0.7 mm Hg with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				placebo and decreased by 3.5 mm Hg with aliskiren (P=0.0045). The mean standing heart rate decreased by 0.3 bpm in the placebo group and increased by 0.7 bpm in the aliskiren group (P=0.466). There were no differences between treatments in any of the other prespecified comparisons, including autonomic measurements, the Kansas City Cardiomyopathy questionnaire, inflammatory and other plasma and urinary biomarkers (including urinary protein excretion), or measurements of glucose/insulin metabolism. Secondary: Not reported

*Agent not available in the United States.
Drug regimen abbreviations: QD=once daily, SR=sustained-release
Study design abbreviations: AC=active comparator, DB=double blind, DD=double dummy, MA=meta-analysis, MC=multicenter, OL=open-label, OS=observational, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized-controlled trial, XO=cross-over
Miscellaneous abbreviations: ABPM=ambulatory blood pressure monitoring, ACE inhibitors=angiotensin converting enzyme inhibitors, ARB=angiotensin II receptor blocker, BMI=body mass index, CAD=coronary artery disease, CHD=coronary heart disease, CI=confidence interval, DBP=diastolic blood pressure, GFR=glomerular filtration rate, HCTZ=hydrochlorothiazide, HTN=hypertension, LVEF=left ventricular ejection fraction, LSM=least squares mean, NYHA=New York Heart Association, RR=relative risk, SBP=systolic blood pressure

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 10. Relative Cost of the Renin Inhibitors

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Aliskiren	tablet	Tekturna®*	$$$$$	$$$$
Combination Products				
Aliskiren and HCTZ	tablet	Tekturna HCT®	$$$$$	$$$$$

*Generic is available in at least one dosage form or strength.
HCTZ=hydrochlorothiazide, N/A=not available

X. Conclusions

Aliskiren is the only renin inhibitor in this class and it is approved for the treatment of hypertension.[6-7] It is available as a single entity product, as well as in combination with hydrochlorothiazide. Aliskiren is available generically.

There are several national and international organizations that have published guidelines on the treatment of hypertension. Guidelines do not address the use of the renin inhibitors.[9-17] Thiazide-type diuretics are frequently recommended as initial therapy in patients with uncomplicated hypertension. According to the National Heart, Lung, and Blood Institute's Eighth Report of The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8), thiazide-type diuretics should be utilized first-line for most patients with hypertension, either alone or in combination with another antihypertensive from a different

medication class (e.g., ACE inhibitors, ARBs, β-blockers, calcium channel blockers).[9] Several guidelines consistently recommend that the selection of an antihypertensive agent be based on compelling indications for use.[9-17] Most patients will require more than one antihypertensive medication to achieve blood pressure goals.[9-17]

Several clinical trials have demonstrated that renin inhibitors effectively lower blood pressure. The reduction in blood pressure with aliskiren monotherapy was similar to monotherapy with ACE inhibitors, angiotensin II receptor blockers, β-blockers, and dihydropyridines. In clinical trials comparing combination therapy to monotherapy, the more aggressive treatment regimen lowered blood pressure to a greater extent than the less-intensive treatment regimen.[20-58] Most patients will require more than one antihypertensive medication to achieved blood pressure goals.[9-17] The use of a fixed-dose combination product may simplify the treatment regimen and improve adherence.[11,12,14] However, there are no prospective, randomized trials that have demonstrated better clinical outcomes with a fixed-dose combination product compared to the coadministration of the individual components as separate formulations. Aliskiren is not recommended for use in combination with ACE inhibitors or ARBs, largely due to the findings of the ALITUTUDE trial in which the risk of renal impairment, hypotension, and hyperkalemia increased in patients with GFR <60 mL/min and patients with diabetes.[6-8,18] Aliskiren has been shown to have positive effects on surrogate markers of cardiovascular and renal damage in patients with type 2 diabetes and nephropathy, heart failure and left ventricular hypertrophy.[55-58] However, the effects of aliskiren on hard cardiovascular and renal endpoints have not been established.

At this time, there is insufficient evidence to conclude that the renin inhibitors offer a significant clinical advantage over other alternatives in general use. Therefore, all brand renin inhibitors within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand renin inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Loop Diuretics
AHFS Class 402808
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I. Overview

Diuretics are commonly used for the treatment of hypertension, heart failure, and various edematous conditions.[1,2] These agents act at different sites within the nephron, which leads to the increased urinary excretion of sodium, chloride and water.[2] The diuretics are categorized into several different AHFS classes, including loop diuretics, potassium-sparing diuretics, thiazide diuretics, thiazide-like diuretics, vasopressin antagonists, and miscellaneous diuretics. The agents which make up these classes differ with regards to their Food and Drug Administration (FDA)-approved indications, mechanism of action, efficacy, safety profiles, tolerability, and ease of use.

The loop diuretics are approved for the treatment of edema and hypertension.[3-7] They primarily act in the thick ascending limb of the loop of Henle to increase the urinary excretion of sodium, chloride, and water. Furosemide and ethacrynic acid also inhibit the absorption of sodium and chloride in the proximal and distal tubules. Bumetanide may also have an additional action in the proximal tubule. The loop diuretics are considered to be the most potent diuretics.[3-8] When given at their maximum dosages, they can lead to the excretion of up to 20% to 25% of the filtered sodium. As renal function declines (glomerular filtration rate <30 mL/minute), a loop diuretic should be considered rather than a thiazide diuretic. Loop diuretics do not possess the added property of arterial vasodilation, as seen with the thiazide diuretics.[1,2] Some studies have suggested that hydrochlorothiazide (a thiazide diuretic) is more effective in lowering blood pressure than the loop diuretics.[9]

The loop diuretics that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All agents are available in a generic formulation. This class was last reviewed in May 2022.

Table 1. Loop Diuretics Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Bumetanide	injection, tablet	N/A	bumetanide
Ethacrynate sodium	injection^	Sodium Edecrin®*	none
Ethacrynic acid	tablet	Edecrin®*	ethacrynic acid
Furosemide	injection, kit, solution, tablet	Furoscix®, Lasix®*	furosemide
Torsemide	tablet	N/A	torsemide

*Generic is available in at least one dosage form or strength.
^Product is primarily administered in an institution.
PDL=Preferred Drug List
N/A=Not available

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the loop diuretics are summarized in Table 2.

Table 2. Treatment Guidelines Using the Loop Diuretics

Clinical Guideline	Recommendation(s)
American Heart Association/American College of Cardiology/ Heart Failure Society of America: **2022 AHA/ACC /HFSA Guideline for the Management of**	Treatment of Stage A heart failure (HF) • Hypertension should be controlled in accordance with guideline-directed medication therapy for hypertension to prevent symptomatic HF. (LoE: A) • In patients with type 2 diabetes and either established CVD or at high cardiovascular risk, SGLT-2 inhibitors should be used to prevent hospitalizations for HF. (LoE: A) • In the general population, healthy lifestyle habits such as regular physical

Clinical Guideline	Recommendation(s)
Heart Failure (2022)[10]	activity, maintaining normal weight, healthy dietary patterns, and avoiding smoking are helpful to reduce future risk of HF. (LoE: B) • Patients at risk of developing HF, natriuretic peptide biomarker-based screening followed by team-based care, including a cardiovascular specialist optimizing therapy, can be useful to prevent the development of LV dysfunction (systolic or diastolic) or new-onset HF. (LoE: B) <u>Treatment of Stage B heart failure</u> • In patients with LVEF≤40%, ACE inhibitors should be used to prevent HF and reduce mortality. (LoE: A) • In patients with a recent or remote history of MI or ACS, statins should be used to prevent symptomatic HF and adverse cardiovascular events. (LoE: A) • In patients with a recent MI and LVEF≤40% who are intolerant to ACE inhibitors, ARB should be used to prevent symptomatic HF and reduce mortality. (LoE: B) • In patients with a recent or remote history of MI or ACS and LVEF≤40%, evidence-based beta blockers should be used to reduce mortality. (LoE: B) • In patients who are at least 40 days post-MI with LVEF ≤30% and NYHA class I symptoms while receiving guideline-directed medication therapy and have reasonable expectation of meaningful survival for greater than one year, an implantable cardioverter-defibrillator is recommended for primary prevention of sudden cardiac death to reduce total mortality. (LoE: B) • In patients with LVEF ≤40%, beta blockers should be used to prevent symptomatic HF. (LoE: C) • In patients with LVEF ≤50%, thiazolidinediones should not be used because they increase the risk of HF, including hospitalizations. (LoE: B) • In patients with LVEF ≤50%, nondihydropyridine calcium channel blockers with negative inotropic effects may be harmful. (LoE: C) <u>Treatment for Stage C Heart Failure with Reduced Ejection Fraction (HFrEF)</u> • For patients with stage C HF, avoiding excessive sodium intake is reasonable to reduce congestive symptoms. (LoE: C) • In patients with HF who have fluid retention, diuretics are recommended to relieve congestion, improve symptoms, and prevent worsening HF. (LoE: B) • For patients with HF and congestive symptoms, addition of a thiazide (e.g., metolazone) to treatment with a loop diuretic should be reserved for patients who do not respond to moderate or high dose loop diuretics to minimize electrolyte abnormalities. (LoE: B) • In patients with HFrEF and NYHA class II to III symptoms, the use of an ARNI is recommended to reduce morbidity and mortality. (LoE: A) • In patients with previous or current symptoms of chronic HFrEF, the use of an ACE inhibitor is beneficial to reduce morbidity and mortality when the use of an ARNI is not feasible. (LoE: A) • In patients with previous or current symptoms of chronic HFrEF, who are intolerant to an ACE inhibitor because of cough or angioedema, and when the use of an ARNI is not feasible, the use of an ARB is recommended to reduce morbidity and mortality. (LoE: A) • In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality. (LoE: B) • ARNIs should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor. (LoE: B) • ARNI or ACE inhibitors should not be administered in patients with a history of angioedema. (LoE: C)

Clinical Guideline	Recommendation(s)
	• In patients with HFrEF, with current or previous symptoms, use of one of the three β-blockers proven to reduce mortality (e.g., bisoprolol, carvedilol, sustained-release metoprolol succinate) is recommended to reduce mortality and hospitalizations. (LoE: A) • In patients with HFrEF and NYHA class II to IV symptoms, a mineralocorticoid receptor antagonist (spironolactone or eplerenone) is recommended to reduce morbidity and mortality, if eGFR is >30 mL/min/1.73 m^2 and serum potassium is <5.0 mEq/L. Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely followed thereafter to minimize risk of hyperkalemia and renal insufficiency. (LoE: A) • In patients taking a mineralocorticoid receptor antagonist whose serum potassium cannot be maintained at <5.5 mEq/L, mineralocorticoid receptor antagonist should be discontinued to avoid life threatening hyperkalemia. (LoE: B) • In patients with symptomatic chronic HFrEF, SGLT-2 an inhibitor is recommended to reduce hospitalization for HF and cardiovascular mortality, irrespective of the presence of type 2 diabetes. (LoE: A) • The combination of hydralazine and isosorbide dinitrate is recommended to improve symptoms and reduce morbidity and mortality for patients self-identified as African Americans with NYHA class III to IV HFrEF receiving optimal therapy. (LoE: A) • In patients with current or previous symptomatic HFrEF who cannot be given first-line agents, such as an ARNI, ACE inhibitor or ARB because of drug intolerance or renal insufficiency, a combination of hydralazine and isosorbide dinitrate might be considered to reduce morbidity and mortality. (LoE: C) • In patients with HF class II to IV symptoms, omega-3 polyunsaturated fatty acid supplementation may be reasonable to use as adjunctive therapy to reduce mortality and cardiovascular hospitalizations. (LoE: B) • In patients with chronic HFrEF without specific indication (e.g., venous thromboembolism, atrial fibrillation, a previous thromboembolic event, or a cardioembolic source, anticoagulation is not recommended. (LoE: B) • Dihydropyridine and non-dihydropyridine calcium channel blockers are not recommended for patients with HFrEF. (LoE: A) • In patients with HFrEF, vitamins, nutritional supplements, and hormonal therapy are not recommended other than to correct specific deficiencies. (LoE: B) • In patients with HFrEF, class IC antiarrhythmic medication and dronedarone may increase risk of mortality. (LoE: A) • In patients with HFrEF, thiazolidinediones increase the risk of worsening HF symptoms and hospitalizations. (LoE: A) • In patients with type 2 diabetes and high cardiovascular risk, the DPP-4 inhibitors, saxagliptin and alogliptin, increase the risk of HF hospitalization and should be avoided in patients with HF. (LoE: B) • In patients with HFrEF, nonsteroidal anti-inflammatory drugs worsen HF symptoms and should be avoided or withdrawn whenever possible. (LoE: B) • For patients with symptomatic (NYHA class II to III) stable chronic HFrEF (LVEF ≤35%) who are receiving guideline-directed medical therapy, including a maximally tolerated dose of a beta blocker, and who are in sinus rhythm with a heart rate of ≥70 beats per minute at rest, ivabradine can be beneficial to reduce HF hospitalizations and cardiovascular death. (LoE: B) • In patients with symptomatic HFrEF despite guideline-directed medical therapy or who are unable to tolerate guideline-directed medical therapy, digoxin might be considered to decrease hospitalizations for HF. (LoE: B) • In select high-risk patients with HFrEF and recent worsening of HF already on guideline-directed medical therapy, an oral soluble guanylate cyclase stimulator (vericiguat) may be considered to reduce HF hospitalization and cardiovascular death. (LoE: B)

Clinical Guideline	Recommendation(s)
	Pharmacological treatment for Stage C HF with mildly reduced EF and improved EF • In patients with HF with mildly reduced EF, SGLT-2 inhibitors can be beneficial in decreasing HF hospitalizations and cardiovascular mortality. (LoE: B) • Among patients with current or previous symptomatic HF with mildly reduced EF (LVEF, 41 to 49%), use of evidence-based beta blockers for HFrEF, ARNI, ACE inhibitor or ARB, and mineralocorticoid receptor antagonists may be considered to reduce the risk of HF hospitalization and cardiovascular mortality, particularly among patients with LVEF on the lower end of this spectrum. (LoE: B) • In patients with HF with improved EF after treatment, guideline-directed medical therapy should be continued to prevent relapse of HF and LV dysfunction, even in patients who may become asymptomatic. (LoE: B) Pharmacological treatment for Stage C HF with preserved EF (HFpEF) • Patients with hypertension and HFpEF should have medication titrated to attain blood pressure targets in accordance with published clinical practice guidelines to prevent morbidity. (LoE: C) • SGLT-2 inhibitors can be beneficial in decreasing HF hospitalizations and cardiovascular mortality. (LoE: B) • In patients with HFpEF, the use of a mineralocorticoid receptor antagonist, ARB, or ARNI may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum. (LoE: B) • Routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or quality of life in patients with HFpEF is ineffective. (LoE: B) Treatment of Stage D (advanced/refractory) HF • For patients with advanced HF and hyponatremia, the benefit of fluid restriction to reduce congestive symptoms is uncertain. (LoE: C) • Continuous intravenous inotropic support is reasonable as "bridge therapy" in patients with HF (Stage D) refractory to guideline-directed medical therapy and device therapy who are eligible for and awaiting mechanical circulatory support or cardiac transplantation. (LoE: B) • In select patients with HF Stage D, despite optimal guideline-directed medical therapy and device therapy who are ineligible for either mechanical circulatory support or cardiac transplantation, continuous intravenous inotropic support may be considered as palliative therapy for symptom control and improvement in functional status. (LoE: B) • Long-term use of either continuous or intermittent, intravenous inotropic agents, for reasons other than palliative care or as a bridge to advanced therapies, is potentially harmful. (LoE: B)
European Society of Cardiology: **Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (2021)**[11]	Pharmacological treatments indicated in patients with (NYHA Class II-IV) heart failure with reduced ejection fraction • An ACE inhibitor is recommended, in addition to a β-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death. • A mineralocorticoid receptor antagonist (MRA) is recommended for patients with HFrEF, who remain symptomatic despite treatment with an ACE inhibitor and a β-blocker, to reduce the risk of HF hospitalization and death. • Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death. Dapagliflozin or empagliflozin are recommended, in addition to optimal medical therapy with an ACE-I/ARNI, a β-blocker and an MRA, for patients with HFrEF regardless of diabetes status. • Sacubitril-valsartan is recommended as a replacement for an ACE inhibitor to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE

Clinical Guideline	Recommendation(s)
	inhibitor, a β-blocker, and a mineralocorticoid receptor antagonist. • Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion. • Ivabradine should be considered to reduce the risk of HF hospitalization or cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm despite treatment with an evidence-based dose of β-blocker (or maximum tolerated dose below that), ACE inhibitor (or ARB), and a mineralocorticoid receptor antagonist (or ARB). • Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm who are unable to tolerate or have contraindications for a β-blocker. Patients should also receive an ACE inhibitor (or ARB) and a mineralocorticoid receptor antagonist (or ARB). • An ARB is recommended to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients unable to tolerate an ACE inhibitor (patients should also receive a β-blocker and mineralocorticoid receptor antagonist). • An ARB may be considered to reduce the risk of HF hospitalization and death in patients who are symptomatic despite treatment with a β-blocker who are unable to tolerate a mineralocorticoid receptor antagonist. • Vericiguat may be considered in patients in NYHA class II-IV who have had worsening HF despite treatment with an ACE-I (or ARNI), a β-blocker and an MRA to reduce the risk of CV mortality or HF hospitalization. • Hydralazine and isosorbide dinitrate should be considered in self-identified black patients with LVEF ≤35% or with an LVEF <45% combined with a dilated LV in NYHA Class III–IV despite treatment with an ACE-I a β-blocker and a mineralocorticoid receptor antagonist to reduce the risk of HF hospitalization and death. • Hydralazine and isosorbide dinitrate may be considered in symptomatic patients with HFrEF who can tolerate neither an ACE inhibitor nor an ARB (or they are contraindicated) to reduce the risk of death. • Digoxin is a treatment with less-certain benefits and may be considered in symptomatic patients in sinus rhythm despite treatment with an ACE inhibitor (or ARB), a β-blocker and a mineralocorticoid receptor antagonist, to reduce the risk of hospitalization (both all-cause and HF-hospitalizations). <u>Recommendations for treatment of patients with (NYHA class II-IV) heart failure with mildly reduced ejection fraction (HFmrEF)</u> • Diuretics are recommended in patients with congestion and HFmrEF in order to alleviate symptoms and signs. • An ACE inhibitor may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • An ARB may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • A β-blocker may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • An MRA may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • Sacubitril/valsartan may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. <u>Recommendations for treatment of patients with heart failure with preserved ejection fraction (HFpEF)</u> • It is recommended to screen patients with HFpEF for both cardiovascular and noncardiovascular comorbidities, which, if present, should be treated provided

Clinical Guideline	Recommendation(s)
	safe and effective interventions exist to improve symptoms, well-being and/or prognosis. • Diuretics are recommended in congested patients with HFpEF in order to alleviate symptoms and signs. <u>Recommendations for the primary prevention of heart failure in patients with risk factors for its development</u> • Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life. • Treatment with statins is recommended in patients at high risk of CV disease or with CV disease in order to prevent or delay the onset of HF, and to prevent HF hospitalizations. • SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with diabetes at high risk of CV disease or with CV disease in order to prevent HF hospitalizations. • Counselling against sedentary habit, obesity, cigarette smoking, and alcohol abuse is recommended to prevent or delay the onset of HF. <u>Recommendations for the initial management of patients with acute heart failure – pharmacotherapy</u> • Intravenous loop diuretics are recommended for all patients with acute HF admitted with signs/symptoms of fluid overload to improve symptoms. It is recommended to regularly monitor symptoms, urine output, renal function and electrolytes during use of intravenous diuretics. • Combination of a loop diuretic with thiazide type diuretic should be considered in patients with resistant oedema who do not respond to an increase in loop diuretic doses. • In patients with acute HF and SBP >110 mmHg, intravenous vasodilators may be considered as initial therapy to improve symptoms and reduce congestion. • Inotropic agents may be considered in patients with SBP <90 mmHg and evidence of hypoperfusion who do not respond to standard treatment, including fluid challenge, to improve peripheral perfusion and maintain end-organ function. • Inotropic agents are not recommended routinely, due to safety concerns, unless the patient has symptomatic hypotension and evidence of hypoperfusion. • A vasopressor, preferably norepinephrine, may be considered in patients with cardiogenic shock to increase blood pressure and vital organ perfusion. • Thromboembolism prophylaxis (e.g. with LMWH) is recommended in patients not already anticoagulated and with no contraindication to anticoagulation, to reduce the risk of deep venous thrombosis and pulmonary embolism. • Routine use of opiates is not recommended, unless in selected patients with severe/intractable pain or anxiety.
Eighth Joint National Committee (JNC 8): **2014 Evidence-based Guideline for the Management of High Blood Pressure in Adults (2014)[12]**	• Pharmacologic treatment should be initiated in patients ≥60 years of age to lower blood pressure at systolic blood pressure ≥150 mm Hg or diastolic blood pressure ≥90 mm Hg and to a goal systolic blood pressure <150 mm Hg and goal diastolic blood pressure <90 mm Hg. Adjustment of treatment is not necessary if treatment results in lower blood pressure and treatment is well tolerated and without adverse effects on health or quality of life. • In patients <60 years of age, pharmacologic treatment should be initiated to lower blood pressure at diastolic blood pressure ≥90 mm Hg to a goal diastolic blood pressure <90 mm Hg. • In patients <60 years of age, pharmacologic treatment should be initiated to lower blood pressure at systolic blood pressure ≥150 mm Hg to a goal diastolic blood pressure <140 mm Hg. • For patients ≥18 years of age with chronic kidney disease or diabetes,

Clinical Guideline	Recommendation(s)
	pharmacologic treatment should be initiated to lower blood pressure at systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg and to a goal systolic blood pressure <140 mm Hg and goal diastolic blood pressure <90 mm Hg. • Initial antihypertensive treatment for the general nonblack population, including those with diabetes, should include thiazide-type diuretic, calcium channel blocker (CCB), ACE inhibitor, or ARB. • Initial antihypertensive treatment for the general black population, including those with diabetes, should include thiazide-type diuretic or CCB. • For patients ≥18 years of age with chronic kidney disease regardless of race or diabetes status, initial (or add-on) treatment should include an ACE inhibitor or ARB to improve kidney outcomes. • The main goal of antihypertensive treatment is to attain and maintain goal blood pressure. • If goal blood pressure is not attained within a month of treatment, the dose of the initial drug should be increased or second drug from the thiazide-type diuretic, CCB, ACE inhibitor, or ARB classes should be added. • If goal is not achieved with two drugs, a third drug from the thiazide-type diuretic, CCB, ACE inhibitor, or ARB classes should be added. • An ACE inhibitor and ARB should not be used together. • Antihypertensive classes can be used if the patient is unable to achieve goal blood pressure with three agents or had a contraindication to a preferred class. • If blood pressure is not able to be achieved or in complicated patients, referral to a hypertension specialist may be indicated.
International Society of Hypertension: **Global Hypertension Practice Guidelines (2020)**[13]	<u>Lifestyle modifications</u> • Lifestyle modification is the first line of antihypertensive treatment. • Salt reduction: Reduce salt added when preparing foods, and at the table. Avoid or limit consumption of high salt foods such as soy sauce, fast foods and processed food including breads and cereals high in salt. • Healthy diet: Eating a diet that is rich in whole grains, fruits, vegetables, polyunsaturated fats and dairy products and reducing food high in sugar, saturated fat and trans fats, such as the DASH diet. • Healthy drinks: Moderate consumption of coffee, green and black tea. Other beverages that can be beneficial include karkadé (hibiscus) tea, pomegranate juice, beetroot juice and cocoa. • Moderation of alcohol consumption: The recommended daily limit for alcohol consumptions is 2 standard drinks for men and 1.5 for women (10 g alcohol/standard drink). Avoid binge drinking. • Weight reduction: Body weight control is indicated to avoid obesity. Particularly abdominal obesity should be managed. Ethnic-specific cut-offs for BMI and waist circumference should be used. Alternatively, a waist-to-height ratio <0.5 is recommended for all populations. • Smoking cessation: Smoking is a major risk factor for cardiovascular disease (CVD), COPD and cancer. Smoking cessation and referral to smoking cessation programs are advised. • Regular physical activity: Studies suggest that regular aerobic and resistance exercise may be beneficial for both the prevention and treatment of hypertension. Moderate intensity aerobic exercise (walking, jogging, cycling, yoga, or swimming) for 30 minutes on five to seven days per week Strength training also can help reduce blood pressure. Performance of resistance/strength exercises on two to three days per week. • Reduce stress and induce mindfulness: Stress should be reduced and mindfulness or meditation introduced into the daily routine. • Reduce exposure to air pollution and cold temperature: Evidence from studies

Clinical Guideline	Recommendation(s)
	support a negative effect of air pollution on blood pressure in the long-term. <u>Pharmacological Treatment</u> • Ideal characteristics of drug treatment o Treatments should be evidence-based in relation to morbidity/mortality prevention. o Use a once-daily regimen which provides 24-hour blood pressure control. o Treatment should be affordable and/or cost-effective relative to other agents. o Treatments should be well-tolerated. o Evidence of benefits of use of the medication in populations to which it is to be applied. • General scheme for drug treatment o Lifestyle modification is the first line of antihypertensive treatment. o Grade 1 hypertension (BP 140 to 159/ 90 to 99): Immediate drug treatment in high-risk patients or those with CVD, chronic kidney disease (CKD), diabetes mellitus (DM), or hypertension-mediated organ damage (HMOD). Drug treatment after three to six months of lifestyle intervention if BP still not controlled in low to moderate risk patients. o Grade 2 hypertension (BP ≥160/100): Immediate drug treatment in all patients. • Core drug-treatment strategy o Step 1: Dual low-dose combination (ACE inhibitor or ARB plus dihydropyridine-calcium channel blockers (DHP-CCB)); consider monotherapy in low-risk grade 1 hypertension or in very old (≥80 years) or frail patients; consider ACE/ARB plus thiazide-like diuretic in post-stroke, very elderly, incipient HF, or CCB intolerance; consider ACE/ARB plus DHP-CCB or DHP-CCB plus thiazide-like diuretics in black patients. o Step 2: Dual full-dose combination (ACE inhibitor or ARB plus DHP-CCB); consider monotherapy in low-risk grade 1 hypertension or in very old (≥80 years) or frail patients; consider ACE/ARB plus thiazide-like diuretic in post-stroke, very elderly, incipient HF, or CCB intolerance. o Step 3: Triple combination (ACE/ARB plus DHP-CCB plus thiazide-like diuretic). o Step 4, resistant hypertension: triple combination plus spironolactone or other drug, alternatives include amiloride, doxazosin, eplerenone, clonidine, or β-blocker. Caution with spironolactone or other potassium sparing diuretics when estimated GFR <45 mL/min/1.73m^2 or K+ >4.5 mmol/L. o Consider β-blockers at any treatment step when there is a specific indications for their use, e.g., heart failure, angina, post-MI, atrial fibrillation, or younger women planning pregnancy or pregnant.
Hypertension Canada: **2020 Guidelines for the Prevention, Diagnosis, Risk Assessment, and Treatment of Hypertension in Adults and Children (2020)**[14]	<u>Indications for drug therapy for adults with hypertension without compelling indications for specific agents</u> • Antihypertensive therapy should be prescribed for average diastolic blood pressure (DBP) measurements of ≥100 mmHg or average systolic blood pressure (SBP) measurements of ≥160 mmHg in patients without macrovascular target organ damage or other cardiovascular risk factors. • Antihypertensive therapy should be strongly considered for average DPB readings ≥90 mmHg or for average SBP readings ≥140 mmHg in the presence of macrovascular target organ damage or other independent cardiovascular risk factors. • For high-risk patients, aged 50 years or older, with SBP levels ≥130 mmHg,

Clinical Guideline	Recommendation(s)

	intensive management to target a SBP <120 mmHg should be considered. Patient selection for intensive management is recommended and caution should be taken in certain high-risk groups.
	
	<u>Indications for drug therapy for adults with diastolic and with or without systolic hypertension</u>
	• Initial therapy should be with either monotherapy or single pill combination (SPC).
	  ○ Recommended monotherapy choices are:
	  ▪ A thiazide/thiazide-like diuretic, with longer-acting diuretics preferred;
	  ▪ A β-blocker (in patients <60 years of age);
	  ▪ An angiotensin-converting enzyme (ACE) inhibitor (in nonblack patients);
	  ▪ An angiotensin receptor blocker (ARB); or
	  ▪ A long-acting calcium channel blocker (CCB).
	  ○ Recommended SPC choices are those in which an ACE inhibitor is combined with a CCB, ARB with a CCB, or ACE inhibitor or ARB with a diuretic.
	  ○ Hypokalemia should be avoided in patients treated with thiazide/thiazide-like diuretic monotherapy.
	• Additional antihypertensive drugs should be used if target BP levels are not achieved with standard-dose monotherapy. Add-on drugs should be chosen from first-line choices. Useful choices include a thiazide/thiazide-like diuretic or CCB with either: ACE inhibitor, ARB, or β-blocker. Caution should be exercised in combining a nondihydropyridine CCB and a β-blocker. The combination of an ACE inhibitor and an ARB is not recommended.
	• If BP is still not controlled with a combination of two or more first-line agents, or there are adverse effects, other antihypertensive drugs may be added.
	• Possible reasons for poor response to therapy should be considered.
	• α-Blockers are not recommended as first-line agents for uncomplicated hypertension; β-blockers are not recommended as first-line therapy for uncomplicated hypertension in patients ≥60 years of age; and ACE inhibitors are not recommended as first-line therapy for uncomplicated hypertension in black patients. However, these agents may be used in patients with certain comorbid conditions or in combination therapy.
	
	<u>Indications for drug therapy for adults with isolated systolic hypertension</u>
	• Initial therapy should be single-agent therapy with a thiazide/thiazide-like diuretic, a long-acting dihydropyridine CCB, or an ARB. If there are adverse effects, another drug from this group should be substituted. Hypokalemia should be avoided in patients treated with thiazide/thiazide-like diuretic monotherapy.
	• Additional antihypertensive drugs should be used if target BP levels are not achieved with standard-dose monotherapy. Add-on drugs should be chosen from first-line options.
	• If BP is still not controlled with a combination of two or more first-line agents, or there are adverse effects, other classes of drugs (such as α-blockers, ACE inhibitors, centrally acting agents, or nondihydropyridine CCBs) may be combined or substituted.
	• Possible reasons for poor response to therapy should be considered.
	• α-Blockers are not recommended as first-line agents for uncomplicated isolated systolic hypertension; and β-blockers are not recommended as first-line therapy for isolated systolic hypertension in patients ≥60 years of age. However, both agents may be used in patients with certain comorbid conditions or in combination therapy.

Clinical Guideline	Recommendation(s)
	Guidelines for hypertensive patients with coronary artery disease (CAD) • For most hypertensive patients with CAD, an ACE inhibitor or ARB is recommended. • For hypertensive patients with CAD, but without coexisting systolic heart failure, the combination of an ACE inhibitor and ARB is not recommended. • For high-risk hypertensive patients, when combination therapy is being used, choices should be individualized. The combination of an ACE inhibitor and a dihydropyridine CCB is preferable to an ACE inhibitor and a thiazide/thiazide-like diuretic in selected patients. • For patients with stable angina pectoris but without previous heart failure, myocardial infarction, or coronary artery bypass surgery, either a β-blocker or CCB can be used as initial therapy. • Short-acting nifedipine should not be used. • When decreasing SBP to target levels in patients with established CAD (especially if isolated systolic hypertension is present), be cautious when the DBP is ≤60 mmHg because of concerns that myocardial ischemia might be exacerbated, especially in patients with left ventricular hypertrophy (LVH). Guidelines for patients with hypertension who have had a recent myocardial infarction • Initial therapy should include a β-blocker as well as an ACE inhibitor. • An ARB can be used if the patient is intolerant of an ACE inhibitor. • CCBs may be used in patients after myocardial infarction when β-blockers are contraindicated or not effective. Nondihydropyridine CCBs should not be used when there is heart failure, evidenced by pulmonary congestion on examination or radiography. Treatment of hypertension in association with heart failure • In patients with systolic dysfunction (ejection fraction <40%), ACE inhibitors and β-blockers are recommended for initial therapy. Aldosterone antagonists (mineralocorticoid receptor antagonists) may be combined in treatment for patients with a recent cardiovascular hospitalization, acute myocardial infarction, elevated B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide level, or New York Heart Association (NYHA) Class II-IV symptoms. Careful monitoring for hyperkalemia is recommended when combining an aldosterone antagonist with ACE inhibitor or ARB treatment. Other diuretics are recommended as additional therapy if needed. Beyond considerations of BP control, doses of ACE inhibitors or ARBs should be titrated to those reported to be effective in trials unless adverse effects become manifest. • An ARB is recommended if ACE inhibitors are not tolerated. • A combination of hydralazine and isosorbide dinitrate is recommended if ACE inhibitors and ARBs are contraindicated or not tolerated. • For hypertensive patients whose BP is not controlled, an ARB may be combined with an ACE inhibitor and other antihypertensive drug treatment. Careful monitoring should be used if combining an ACE inhibitor and an ARB because of potential adverse effects such as hypotension, hyperkalemia, and worsening renal function. Additional therapies may also include dihydropyridine CCBs. • An angiotensin receptor-neprilysin inhibitor (ARNI) should be used in place of an ACE inhibitor or ARB for patients with HFrEF (<40%) who remain symptomatic despite treatment with appropriate dose of guideline directed HF therapy. Eligible patients must have a serum potassium <5.2 mmol/L, an eGFR ≤30 mL/min/1.73m^2 and close surveillance of serum potassium and creatinine. Treatment of hypertension in association with stroke

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	• BP management in acute ischemic stroke (onset to 72 hours)
	  ○ Please refer to Stroke Best Practice recommendations.
	• BP management after acute ischemic stroke
	  ○ Strong consideration should be given to the initiation of antihypertensive therapy after the acute phase of a stroke or transient ischemic attack.
	  ○ After the acute phase of a stroke, BP-lowering treatment is recommended to a target of consistently <140/90 mmHg.
	  ○ Treatment with an ACE inhibitor and thiazide/thiazide-like diuretic combination is preferred.
	  ○ For patients with stroke, the combination of an ACE inhibitor and ARB is not recommended.
	• BP management in hemorrhagic stroke (onset to 72 hours)
	  ○ Please refer to Stroke Best Practice recommendations.
	
	<u>Treatment of hypertension in association with LVH</u>
	• Hypertensive patients with LVH should be treated with antihypertensive therapy to decrease the rate of subsequent cardiovascular events.
	• The choice of initial therapy can be influenced by the presence of LVH. Initial therapy can be drug treatment using ACE inhibitors, ARBs, long-acting CCBs, or thiazide/thiazide-like diuretics. Direct arterial vasodilators such as hydralazine or minoxidil should not be used.
	
	<u>Treatment of hypertension in association with nondiabetic chronic kidney disease</u>
	• Individualize BP targets in patients with chronic kidney disease. Consider intensive targets (SBP <120 mmHg) in appropriate patients.
	• For patients with hypertension and proteinuric chronic kidney disease (urinary protein >150 mg per 24 hours or albumin to creatinine ratio >30 mg/mmol), initial therapy should be an ACE inhibitor or an ARB if there is intolerance to ACE inhibitors.
	• In most cases, combination therapy with other antihypertensive agents might be needed to reach target BP levels.
	• The combination of an ACE inhibitor and ARB is not recommended for patients with nonproteinuric chronic kidney disease.
	
	<u>Treatment of hypertension in association with renovascular disease</u>
	• Patients with hypertension attributable to atherosclerotic renal artery stenosis should be primarily medically managed because renal angioplasty and stenting offers no benefit over optimal medical therapy alone.
	• Renal artery angioplasty and stenting for atherosclerotic hemodynamically significant renal artery stenosis could be considered for patients with uncontrolled hypertension resistant to maximally tolerated pharmacotherapy, progressive renal function loss, and acute pulmonary edema.
	• Patients with confirmed renal fibromuscular dysplasia (FMD) should be referred to a hypertension specialist.
	• Renal artery angioplasty without stenting is recommended for treatment of FMD-related renal artery stenosis. Stenting is not recommended unless needed because of a periprocedural dissection. Surgical revascularization should be considered in cases of complex lesions less amendable to angioplasty, stenosis associated with complex aneurysm, and restenosis despite two unsuccessful attempts of angioplasty.
	
	<u>Treatment of hypertension in association with diabetes mellitus</u>
	• Persons with diabetes mellitus should be treated to attain SBP of <130 mmHg and DBP of <80 mmHg.
	• For persons with cardiovascular or kidney disease, including microalbuminuria,

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	or with cardiovascular risk factors in addition to diabetes and hypertension, an ACE inhibitor or an ARB is recommended as initial therapy. • For persons with diabetes and hypertension not included in other guidelines in this section, appropriate choices include (in alphabetical order): ACE inhibitors, ARBs, dihydropyridine CCBs, and thiazide/thiazide-like diuretics. • If target BP levels are not achieved with standard-dose monotherapy, additional antihypertensive therapy should be used. For persons in whom combination therapy with an ACE inhibitor is being considered, a dihydropyridine CCB is preferable to a thiazide/thiazide-like diuretic. <u>Resistant hypertension</u> • Resistant hypertension is defined as BP above target despite three or more BP-lowering drugs at optimal doses preferably including a diuretic (and usually a renin-angiotensin-aldosterone system blocker and a CCB. • Accurate office and out-of-office BP measurement is essential. • Other reasons for apparent resistant hypertension should be eliminated before diagnosing true resistant hypertension, including nonadherence, white coat effect, and secondary hypertension. • Pharmacotherapy with the additional use of spironolactone, bisoprolol, doxazosin, amiloride, eplerenone, or clonidine with the baseline regimen decreases BP significantly, with the greatest BP-lowering shown with spironolactone. • Patients with resistant hypertension should be referred to providers with expertise in diagnosis and management of hypertension. <u>Hypertension and pediatrics</u> • BP should be measured regularly in children three years of age or older; the auscultatory method is the gold-standard at present. • Initial therapy should be monotherapy, with an ACE inhibitor or ARB (not first-line in black children), or a long-acting dihydropyridine CCB. • The treatment t goal is systolic and diastolic office BP and/or ABPM < 95th percentile or <90th percentile in children with risk factors or target organ damage. • Complex cases should be referred to an expert in pediatric hypertension. <u>Hypertension and pregnancy</u> • Up to 7% of pregnancies are complicated by a hypertensive disorder of pregnancy, and approximately 5% of women will have chronic hypertension when they become pregnant. • The prevalence of hypertension in pregnancy is expected to increase with women becoming pregnant later in their reproductive years and the increasing prevalence of cardiovascular comorbidities such as increased preconception body mass index and maternal diabetes. • The possibility of pregnancy should be considered when managing women with hypertension who are of reproductive age. • Preconception counselling should be offered to all women with hypertension who are considering pregnancy. • ACE inhibitor and ARB therapy should be avoided before conception and during pregnancy unless there is a compelling indication for their use (i.e., proteinuric kidney disease). • Hypertension during pregnancy can increase the risk of adverse maternal and fetal outcomes, including an increased risk of preeclampsia, placental abruption, prematurity, small for gestational age infants, stillbirth, and maternal renal and retinal injury, thus generally requires involvement of an interdisciplinary team including obstetrical care providers.

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	• Antihypertensive therapy is recommended for average SBP measurements of ≥140 mmHg or DBP measurements of ≥90 mmHg in pregnant women with chronic hypertension, gestational hypertension, or preeclampsia. Initial antihypertensive therapy should be monotherapy from the following first-line drugs: oral labetalol, oral methyldopa, long-acting oral nifedipine, or other oral b-blockers (acebutolol, metoprolol, pindolol, and propranolol). Other antihypertensive drugs can be considered as second-line drugs including: clonidine, hydralazine, and thiazide diuretics. • Women with severe hypertension with SBP ≥160 mmHg or DBP ≥110 mmHg in pregnancy or postpartum require urgent antihypertensive therapy because it is considered an obstetrical emergency. • Antihypertensive drugs used in breastfeeding women include: labetalol, methyldopa, long-acting nifedipine, enalapril, or captopril.
European Society of Hypertension: **2023 Guidelines for the management of arterial hypertension (2023)[15]**	General recommendations for antihypertensive drug treatment • BP lowering should be prioritized over the selection of specific antihypertensive drug classes because treatment benefit largely originates from BP reduction. • Five major drug classes including, ACE inhibitors, ARBs, β-blockers, CCBs, and Thiazide/Thiazide-like diuretics have effectively reduced blood pressure and cardiovascular events in randomized controlled trials. These drugs and their combinations are recommended as the basis of antihypertensive treatment strategies. • Initiation of therapy with a two-drug combination is recommended for most hypertensive patients. Preferred combinations should comprise a RAS blocker (either an ACE inhibitor or an ARB) with a CCB or thiazide/thiazide-like diuretic. Other combinations of the five major drug classes can be used. • Initiation with monotherapy can be considered in patients with: grade 1 hypertension and low-risk if BP is only marginally elevated (less than 150 mmHg SBP and 95 mmHg DBP) high-normal BP and very high cardiovascular risk, frailty and/or and advance age. • If BP is not controlled with the initial two-drug combination by using the maximum recommended and tolerated dose of the respective components, treatment should be increased to a three-drug combination, usually a RAS blocker plus CCB plus thiazide/thiazide-like diuretic. • If BP is not controlled with a three-drug combination by using the maximum recommended and tolerated dose of the respective components, it is recommended to extend treatment according to the recommendations for resistant hypertension. • The use of single pill combinations should be preferred at any treatment step (i.e. during initiation of therapy with a two-drug combination and at any other step of treatment). • β-blocker should be used at initiation of therapy or at any treatment step as guideline-directed medical therapy (e.g., heart failure with reduced ejection fraction, anti-ischemic therapy in chronic coronary syndromes, heart rate control in atrial fibrillation). • β-blockers can be considered in the presence of several other conditions in which their use can be favorable. • The combination of two RAS blockers is not recommended due to increased risk of adverse events, in particular AKI. True-resistant hypertension • In resistant hypertension, it is recommended to reinforce lifestyle measures. • Drugs that can be considered as additional therapy in patients with resistant hypertension are preferably spironolactone (or other MRA), or β-blocker or Alpha-1 blockers or centrally acting agents (clonidine), or amiloride. • Thiazide/thiazide-like diuretics are recommended in resistant hypertension if

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	estimated eGFR is ≥30 mL/min/1.73m^2. • Loop diuretics may be considered in patients with an estimated eGFR < 45 mL/min/1.73m^2 and should be used if eGFR falls below 30 mL/min/1.73m^2. • Chlorthalidone (12.5 to 25 mg once daily) could be used with or without a loop diuretic if eGFR is <30 mL/min/1.73m^2. • Renal deprivation can be considered as an additional treatment option in patients with resistant hypertension if eGFR is >40 mL/min/1.73m^2. • Patients with resistant hypertension should be followed very closely. Follow-up includes periodical ambulatory blood pressure monitoring and assessment of hypertension-mediated organ damage, particularly kidney function and serum potassium levels. Regular use of home blood pressure monitoring and monitoring of drug adherence are desirable.
National Institute for Health and Clinical Excellence: **Hypertension in adults: diagnosis and management (2019)**[16]	Choosing antihypertensive drug treatment (for people with or without type II diabetes) • Where possible, recommend treatment with drugs taken only once a day. • Prescribe non-proprietary drugs where these are appropriate and minimize cost. • Offer people with isolated systolic hypertension (systolic blood pressure ≥160 mmHg) the same treatment as people with both raised systolic and diastolic blood pressure. • Offer antihypertensive drug treatment to women of child-bearing potential with diagnosed hypertension in line with recommendations in this guideline. For women considering pregnancy or who are pregnant or breastfeeding, manage hypertension in line with the recommendations on Management of pregnancy with chronic hypertension and Breastfeeding in 'Hypertension in pregnancy'. • When choosing antihypertensive drug treatment for adults of black African or African-Caribbean family origin, consider an angiotensin II receptor blocker, in preference to an angiotensin-converting enzyme inhibitor. Step one treatment • Patients <55 years of age should be offered a step one antihypertensive with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). • Offer an ACE inhibitor or an ARB to adults starting step 1 antihypertensive treatment who have type II diabetes and are of any age or family origin or those aged <55 years but not of black African or African-Caribbean family origin. • If an ACE inhibitor is not tolerated, offer an ARB. • Do not combine an ACE inhibitor with an ARB for the treatment of hypertension. • Offer a calcium channel blocker (CCB) to adults starting step 1 antihypertensive treatment who are >55 years of age and do not have diabetes and are of black African or African-Caribbean family origin and do not have type II diabetes and of any age. • If a CCB is not suitable, for example because of edema or intolerance, or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic. • If diuretic treatment is to be initiated or changed, offer a thiazide‑like diuretic, such as indapamide in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide. • For adults with hypertension who are already receiving treatment with bendroflumethiazide or hydrochlorothiazide, who have stable, well-controlled blood pressure, continue with their treatment. Step two treatment

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	• Before considering next step treatment for hypertension discuss with the person if they are taking their medicine as prescribed and support adherence in line with NICE's guideline on "Medicines adherence: involving patients decisions about prescribed medicines and supporting adherence". • If hypertension is not controlled with a step one treatment of an ACE inhibitor or ARB, offer choice of one of the following drugs in addition to the step one treatment: a CCB or a thiazide-like diuretic. • If hypertension is not controlled in adults taking step one treatment of a CCB, offer the choice of one of the following drugs in addition to the step one treatment: an ACE inhibitor or an ARB or a thiazide-like diuretic. • If hypertension is not controlled in adults of black African or African–Caribbean family origin who do not have type 2 diabetes taking step one treatment, consider an ARB, in preference to an ACE inhibitor, in addition to step one treatment. <u>Step three treatment</u> • Before considering step three treatment, review the person's medications to ensure they are being taken at the optimal doses and discuss adherence (see recommendation under step two). • If hypertension is not controlled in adults taking step two treatment, offer a combination of an ACE inhibitor or ARB and a CCB and a thiazide-like diuretic. <u>Step four treatment</u> • If hypertension is not controlled in adults taking the optimal tolerated doses of an ACE inhibitor or an ARB plus a CCB and a thiazide-like diuretic, regard them as having resistant hypertension. • Before considering further treatment for a person with resistant hypertension, confirm elevated clinic blood pressure measurements using ambulatory or home blood pressure recordings, assess for postural hypotension, and discuss adherence. • For people with confirmed resistant hypertension, consider adding a fourth antihypertensive drug as step four treatment or seeking specialist advice. • Consider further diuretic therapy with low-dose spironolactone for adults with resistant hypertension starting step four treatment who have a blood potassium level of 4.5 mmol/l or less. Use particular caution in people with a reduced estimated glomerular filtration rate because they have an increased risk of hyperkalemia. • When using further diuretic therapy for step four treatment of resistant hypertension, monitor blood sodium and potassium and renal function within one month of starting treatment and repeat as needed thereafter. • Consider an alpha-blocker or beta-blocker for adults with resistant hypertension starting step four treatment who have a blood potassium level of more than 4.5 mmol/l. • If blood pressure remains uncontrolled in people with resistant hypertension taking the optimal tolerated doses of four drugs, seek specialist advice.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in Blacks (2010)[17]**	• To attain and maintain blood pressure (BP) below target levels, multiple antihypertensive drugs will be required in most hypertensive blacks. • Use of two-drug combination therapy when SBP is >15 mm Hg and/or DBP is >10 mm Hg above goal levels is increasingly recommended as first-line therapy. • Two-drug regimens have generally contained a thiazide-type diuretic; however, the combination of a calcium channel blocker (CCB) with either an ACE inhibitor or an ARB has been shown equally efficacious in BP lowering but with demonstrated superiority (CCB+ACE) for hard clinical outcomes compared with the same ACE inhibitor plus a thiazide-type diuretic. • In secondary prevention patients, the combination therapy should include a drug(s) with the appropriate compelling indications.

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	• Certain classes of antihypertensive medications, specifically diuretics and CCBs, lower BP on average more than β-blockers and renin-angiotensin system (RAS) blockers in black patients when used as monotherapies. • In the absence of compelling indications, when BP is near goal levels, monotherapy with a diuretic or a CCB is preferred. • Lifestyle modifications should be initiated in all patients with hypertension, whether or not pharmacotherapy is planned. • ACE inhibitors or ARBs are recommended as alternative monotherapy options in the treatment of hypertension in blacks. The rationale for their lower tier monotherapy recommendation is because they have consistently achieved lesser average reductions in BP relative to that observed with monotherapy using either a diuretic or CCB.
Kidney Disease Improving Clinical Outcomes Group: **KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease (2021)**[18]	<u>Blood pressure measurement</u> • The Work Group recommends standardized office blood pressure (BP) measurement in preference to routine office BP measurements for the management of high BP in adults. • The Work Group suggests that out-of-office BP measurements with ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM) be used to complement standardized office BP readings for the management of high BP. <u>Lifestyle interventions for lowering BP in patients with chronic kidney disease (CKD) not receiving dialysis</u> • The Work Group suggests targeting a sodium intake <2 grams of sodium per day (or <90 mmol of sodium per day, or <5 grams of sodium chloride per day) in patients with high BP and CKD. • The Work Group suggests that patients with high BP and CKD be advised to undertake moderate-intensity physical activity for a cumulative duration of at least 150 minutes per week, or to a level compatible with their cardiovascular and physical tolerance. <u>BP management in patients with CKD, with or without diabetes, not receiving dialysis</u> • The Work Group suggests that adults with high BP and CKD be treated with a target systolic BP (SBP) of <120 mmHg, when tolerated, using standardized office BP measurement. • The Work Group recommends starting renin-angiotensin-system inhibitors (RASi) (angiotensin-converting enzyme inhibitor [ACEi] or angiotensin II receptor blocker [ARB]) for people with high BP, CKD, and severely increased albuminuria without diabetes. • The Work Group suggests starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately increased albuminuria without diabetes. • The Work Group recommends starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately-to-severely increased albuminuria with diabetes. • The Work Group recommends avoiding any combination of ACEi, ARB, and direct renin inhibitor (DRI) therapy in patients with CKD, with or without diabetes. <u>BP management in kidney transplant recipients</u> • Treat adult kidney transplant recipients with high BP to a target BP of <130 mmHg systolic and <80 mmHg diastolic using standardized office BP measurement. • The Work Group recommends that a dihydropyridine calcium channel blocker (CCB) or an ARB be used as the first-line antihypertensive agent in adult kidney transplant recipients.

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	BP management in children with CKD • The Work Group suggests that in children with CKD, 24-hour mean arterial pressure by ABPM should be lowered to <50th percentile for age, sex, and height.
American College of Cardiology/ American Heart Association Task Force: **Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults (2017)[19]**	Initiation of Blood Pressure (BP) Treatment for Overall Cardiovascular Disease (CVD) Risk • Use of BP-lowering medications is recommended for secondary prevention of recurrent CVD events in patients with clinical CVD and an average systolic blood pressure (SBP) ≥130 mmHg or an average diastolic blood pressure (DBP) of ≥80 mmHg and for primary prevention in adults with an estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk of ≥10% and an average SBP of ≥130 mmHg or an average ≥80 mmHg. • Use of BP-lowering medication is recommended for primary prevention of CVD in adults with no history of CVD and with an estimated 10-year ASCVD risk <10% and an SBP of ≥140 mmHg or a DBP of ≥90 mmHg. • Simultaneous use of an angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), and/or renin inhibitor is potentially harmful and is not recommended to treat adults with hypertension. • For adults with confirmed hypertension and known CVD or 10-year ASCVD risk of ≥10%, a BP target <130/80 mmHg is recommended. For adults with confirmed hypertension without additional markers of increased CVD risk, a BP target <130/80 mmHg may be reasonable. • For initiation of antihypertensive drug therapy, first-line agents include thiazide diuretics, calcium channel blockers (CCBs), and ACE inhibitors or ARBs. • Initiation of antihypertensive drug therapy with two first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended in adults with stage 2 hypertension and an average BP >20/10 mmHg above their BP target. • Initiation of antihypertensive drug therapy with a single antihypertensive drug is reasonable in adults with stage 1 hypertension and BP goal <130/80 mmHg with dosage titration and sequential addition of other agents to achieve the BP target. Stable Ischemic Heart Disease (SIHD) • In adults with SIHD and hypertension, a BP target <130/80 is recommended. • Adults with SIHD and hypertension (BP ≥130/80 mmHg) should be treated with medications [e.g., guideline-directed medical therapy (GDMT) beta-blockers, ACE inhibitors, or ARBs] for compelling indications [e.g., previous myocardial infarction (MI), stable angina] as first-line therapy, with the addition of other drugs (e.g., dihydropyridine CCBs, thiazide diuretics, and/or mineralocorticoid receptor antagonists) as needed to further control hypertension. • In adults with SIHD with angina and persistent uncontrolled hypertension, the addition of dihydropyridine CCBs to GDMT beta-blockers is recommended. • In adults who have had a MI or acute coronary syndrome, it is reasonable to continue GDMT beta-blockers beyond three years as long-term therapy for hypertension. • Beta-blockers and/or CCBs might be considered to control hypertension in patients with coronary artery disease (CAD) had an MI more than three years ago and have angina. Heart Failure • In adults with increased risk of HF, the optimal BP in those with hypertension should be <130 mmHg. • Adults with HFrEF and hypertension should be prescribed GDMT titrated to attain a BP <130/80 mmHg. • Non-dihydropyridine CCBs are not recommended in the treatment of hypertension in adults with HFrEF.

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	• In adults with HFpEF who present with symptoms of volume overload, diuretics should be prescribed to control hypertension. • Adults with HFpEF and persistent hypertension after management of volume overload should be prescribed ACE inhibitors or ARBs and beta-blockers titrated to attain SBP <130 mmHg. CKD • Adults with hypertension and CKD should be treated to a BP goal <130/80 mmHg. • In adults with hypertension and CKD [stage 3 or higher or stage 1 or 2 with albuminuria (≥300 mg/d, or ≥300 mg/g albumin-to-creatinine ratio or the equivalent in the first morning void)], treatment with an ACE inhibitor is reasonable to slow kidney disease progression. Treatment with an ARB may be reasonable if an ACE inhibitor is not tolerated. • After kidney transplantation, it is reasonable to treat patients with hypertension to a BP goal <130/80 mmHg and with a CCB on the basis of improved glomerular filtration rate (GFR) and kidney survival. Cerebrovascular Disease • In adults with intracerebral hemorrhage (ICH) who present with SBP >220 mmHg, it is reasonable to use continuous intravenous (IV) drug infusion and close BP monitoring to lower levels. Immediate lowering of SBP to <140 mmHg in adults with spontaneous ICH who present within six hours of the acute event and have an SBP between 150 mmHg and 220 mmHg is not of benefit to reduce death or severe disability and can be potentially harmful. • Adults with acute ischemic stroke and elevated BP who are eligible for treatment with IV tissue plasminogen activator (tPA) should have their BP slowly lowered to <185/110 mmHg before thrombolytic therapy is initiated. • In adults with an acute ischemic stroke, BP should be <185/110 mmHg before administration of IV tPA and should be maintained below 180/105 mmHg for at least the first 24 hours after initiation drug therapy. • Starting or restarting antihypertensive therapy during hospitalization in patients with BP >140/90 mmHg who are neurologically stable is safe and reasonable to improve long-term BP control, unless contraindicated. • In patient with BP ≥220/120 mmHg who did not receive IV alteplase or endovascular treatment and have no comorbid conditions requiring acute antihypertensive treatment, the benefit of initiating or reinitiating treatment of hypertension within the first 48 to 72 hours is uncertain. It might be reasonable to lower BP by 15% during the first 24 hours after onset of stroke. In patients with BP <220/120 mmHg with the same conditions, initiating or reinitiating treatment of hypertension within the first 48 to 72 hours after an acute ischemic stroke is not effective to prevent death or dependency. • Adults with previously treated stroke or transient ischemic attack should be restarted on antihypertensive treatment after the first few days of the index event to reduce the risk of recurrent stroke and other vascular events. Treatment with a thiazide diuretic, ACE inhibitor, or ARB, or combination treatment consisting of a thiazide diuretic plus ACE inhibitor, is useful. • Adults not previously treated for hypertension who experienced a stroke or transient ischemic attack and have an established BP ≥140/90 mmHg should be prescribed antihypertensive treatment a few days after the index event to reduce the risk of recurrent stroke and other vascular event. • For adults who experience a stroke or transient ischemic attack, selection of specific drugs should be individualized on the basis of patient comorbidities and agent pharmacological class. • For adults who experience a stroke or transient ischemic attack, a BP goal

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	<130/80 mmHg may be reasonable. • For adults with a lacunar stroke, a target SBP goal <130 mmHg may be reasonable. • In adults previously untreated for hypertension who experience an ischemic stroke or transient ischemic attack and have an SBP <140 mmHg and a DBP <90 mmHg, the usefulness of initiating antihypertensive treatment is not well established. Peripheral Artery Disease (PAD) • Adults with hypertension and PAD should be treated similarly to patients with hypertension without PAD. Diabetes Mellitus (DM) • In adults with DM and hypertension, antihypertensive drug treatment should be initiated at a BP of ≥130/80 mmHg with a treatment goal <130/80 mmHg. • In adults with DM and hypertension, all first-line classes of antihypertensive agents (i.e., diuretics, ACE inhibitors, ARBs, and CCBs) are useful and effective. • In adults with DM and hypertension, ACE inhibitors or ARBs may be considered in the presence of albuminuria. Atrial Fibrillation, Valvular Heart Disease, and Aortic disease • Treatment of hypertension can be useful for prevention of recurrence of AF. • In adults with asymptomatic aortic stenosis, hypertension should be treated with pharmacotherapy, starting at a low dose and gradually titrating upward as needed. • In patients with chronic aortic insufficiency, treatment of systolic hypertension with agents that do not slow the heart rate (i.e., avoid beta-blockers) is reasonable. • Beta-blockers are recommended as the preferred antihypertensive agents in patients with hypertension and thoracic aortic disease. Racial and Ethnic Differences in Treatment • In black adults with hypertension but without HF or CKD, including those with DM, initial antihypertensive treatment should include a thiazide-type diuretic or CCB. Two or more antihypertensive medications are recommended to achieve a BP target <130/80 mmHg in most adults with hypertension, especially in black adults with hypertension. Pregnancy • Women with hypertension who become pregnant, or are planning to become pregnant, should be transitioned to methyldopa, nifedipine, and/or labetalol during pregnancy. • Women with hypertension who become pregnant should not be treated with ACE inhibitors, ARBs, or direct renin inhibitors. Older Persons • Treatment of hypertension with an SBP treatment goal <130 mmHg is recommended for noninstitutionalized ambulatory community-dwelling adults (≥65 years of age) with an average SBP of ≥130 mmHg. • For older adults (≥65 years of age) with hypertension and a higher burden of comorbidity and limited life expectancy, clinical judgment, patient preference, and a team-based approach to assess risk/benefit is reasonable for decisions regarding intensity of BP lowering and choice of antihypertensive drugs. Hypertensive Crises • In adults with a hypertensive emergency, admission to an intensive care unit is

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	recommended for continuous monitoring of BP and target organ damage and for parenteral administration of an appropriate agent. • For adults with a compelling condition (i.e., aortic dissection, severe pre-eclampsia or eclampsia, or pheochromocytoma crisis), SBP should be reduced to <140 mmHg during the first hour and to <120 mmHg in aortic dissection. • For adults without a compelling condition, SBP should be reduced by no more than 25% within the first hours; then, if stable, to 160/100 mmHg within the next two to six hours; and then cautiously to normal during the following 24 to 48 hours. Cognitive Decline and Dementia • In adults with hypertension, BP lowering is reasonable to prevent cognitive decline and dementia. Patients Undergoing Surgical Procedures • In patients with hypertension undergoing major surgery who have been on beta-blockers chronically, beta-blockers should be continued. • In patients with hypertension undergoing planned elective major surgery, it is reasonable to continue medical therapy for hypertension until surgery. • In patients with hypertension undergoing major surgery, discontinuation of ACE inhibitors or ARBs perioperatively may be considered. • In patients with planned elective major surgery and SBP ≥180 mmHg or DBP ≥110 mmHg, deferring surgery may be considered. • For patients undergoing surgery, abrupt pre-operative discontinuation of beta-blockers or clonidine is potentially harmful. • Beta-blockers should not be started on the day of surgery in beta-blocker-naïve patients. • Patients with intraoperative hypertension should be managed with IV medications until such time as oral medications can be resumed.
American Diabetes Association: **Standards of Medical Care in Diabetes (2023)**[20]	Hypertension/blood pressure control • Blood pressure should be measured at every routine visit. When possible, patients found to have elevated blood pressure (systolic blood pressure 120 to 129 mmHg and diastolic <80 mmHg) should have blood pressure confirmed using multiple readings, including measurements on a separate day, to diagnose hypertension. Patients with blood pressure ≥180/110 and cardiovascular disease could be diagnosed with hypertension at a single visit. • All hypertensive patients with diabetes should monitor their blood pressure at home. • For patients with diabetes and hypertension, blood pressure targets should be individualized through a shared decision-making process that addresses cardiovascular risk, potential adverse effects of antihypertensive medications, and patient preferences. • Individuals with diabetes and hypertension qualify for antihypertensive drug therapy when the blood pressure is persistently elevated ≥130/80 mmHg. The on-treatment target blood pressure goal is <130/80 mmHg, if it can be safely attained. • In pregnant patients with diabetes and preexisting hypertension, a blood pressure target of 110 to 135/85 is suggested in the interest of reducing the risk for accelerated maternal hypertension and minimizing impaired fetal growth. • For patients with blood pressure >120/80, lifestyle intervention consists of weight loss when indicated, a Dietary Approaches to Stop Hypertension (DASH)-style eating pattern including reducing sodium and increasing potassium intake, moderation of alcohol intake, and increased physical activity. • Patients with confirmed office-based blood pressure ≥130/80 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of

Clinical Guideline	Recommendation(s)
	pharmacologic therapy to achieve blood pressure goals. • Patients with confirmed office-based blood pressure ≥160/100 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of two drugs or a single pill combination of drugs demonstrated to reduce cardiovascular events in patients with diabetes. • Treatment for hypertension should include drug classes demonstrated to reduce cardiovascular events in patients with diabetes (ACE inhibitors, angiotensin receptor blockers, thiazide-like diuretics, or dihydropyridine calcium channel blockers). ACE inhibitors or angiotensin receptor blockers are recommended first-line therapy for hypertension in people with diabetes and coronary artery disease. • Multiple-drug therapy is generally required to achieve blood pressure targets (but not a combination of ACE inhibitors and angiotensin receptor blockers). • An ACE inhibitor or angiotensin receptor blocker, at the maximum tolerated dose indicated for blood pressure treatment, is the recommended first-line treatment for hypertension in patients with diabetes and urinary albumin–to–creatinine ratio ≥300 mg/g creatinine or 30 to 299 mg/g creatinine. If one class is not tolerated, the other should be substituted. • For patients treated with an ACE inhibitor, angiotensin receptor blocker, or diuretic, serum creatinine/estimated glomerular filtration rate and serum potassium levels should be monitored at least annually. • Patients with hypertension who are not meeting blood pressure targets on three classes of antihypertensive medications (including a diuretic) should be considered for mineralocorticoid receptor antagonist therapy. <u>Chronic kidney disease</u> • At least once a year, assess urinary albumin (e.g., spot urinary albumin–to–creatinine ratio) and estimated glomerular filtration rate in patients with type 1 diabetes with duration of five or more years and in all patients with type 2 diabetes. • In people with established diabetic kidney disease, urinary albumin (e.g., spot urinary albumin-to-creatinine ratio) and estimated glomerular filtration rate should be monitored one to four times per year depending on the stage of the disease. Optimize glucose control to reduce the risk or slow the progression of chronic kidney disease (CKD). • For patients with type 2 diabetes and diabetic kidney disease, use of a sodium-glucose cotransporter 2 inhibitor in patients with an estimated glomerular filtration rate ≥20 mL/min/1.73 m^2 and urinary albumin ≥200 mg/g creatinine is recommended to reduce CKD progression and cardiovascular events. • For patients with type 2 diabetes and diabetic kidney disease, use of a sodium–glucose cotransporter 2 inhibitor is recommended to reduce chronic kidney disease progression and cardiovascular events in patients with an estimated glomerular filtration rate ≥20 mL/min/1.73 m^2 and urinary albumin ranging from normal to 200 mg/g creatinine. • In people with type 2 diabetes and diabetic kidney disease, consider use of sodium–glucose cotransporter 2 inhibitors (if estimated glomerular filtration rate is ≥20 mL/min/1.73 m^2), a glucagon-like peptide 1 agonist, or a nonsteroidal mineralocorticoid receptor antagonist (if estimated glomerular filtration rate is ≥25 mL/min/1.73 m^2) additionally for cardiovascular risk reduction. • In people with chronic kidney disease and albuminuria who are at increased risk for cardiovascular events or chronic kidney disease progression, a nonsteroidal mineralocorticoid receptor antagonist shown to be effective in clinical trials is recommended to reduce chronic kidney disease progression and cardiovascular events. • Optimize blood pressure control and reduce blood pressure variability to reduce

Clinical Guideline	Recommendation(s)
	the risk or slow the progression of CKD. • Do not discontinue renin-angiotensin system blockade for minor increases in serum creatinine (≤30%) in the absence of volume depletion. • For people with nondialysis-dependent stage 3 or higher CKD, dietary protein intake should be a maximum of 0.8 g/kg body weight per day (the recommended daily allowance). For patients on dialysis, higher levels of dietary protein intake should be considered, since protein energy wasting is a major problem in some dialysis patients. • In nonpregnant patients with diabetes and hypertension, either an ACE inhibitor or an angiotensin receptor blocker is recommended for those with modestly elevated urinary albumin–to–creatinine ratio (30 to 299 mg/g creatinine) and is strongly recommended for those with urinary albumin–to–creatinine ratio ≥300 mg/g creatinine and/or estimated glomerular filtration rate <60 mL/min/1.73 m^2. • Periodically monitor serum creatinine and potassium levels for the development of increased creatinine and hyperkalemia when ACE inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists are used, or hypokalemia when diuretics are used. • An ACE inhibitor or an angiotensin receptor blocker is not recommended for the primary prevention of CKD in patients with diabetes who have normal blood pressure, normal urinary albumin–to–creatinine ratio (<30 mg/g creatinine), and normal estimated glomerular filtration rate. • Patients should be referred for evaluation by a nephrologist if they have continuously increasing urinary albumin levels and/or continuously decreasing estimated glomerular filtration rate and an estimated glomerular filtration rate <30 mL/min/1.73 m^2. • Promptly refer to a nephrologist for uncertainty about the etiology of kidney disease, difficult management issues, and rapidly progressing kidney disease.
American Association for the Study of Liver Diseases: **Diagnosis, Evaluation, and Management of Ascites, Spontaneous Bacterial Peritonitis and Hepatorenal Syndrome: 2021 Practice Guidance (2021)**[21]	Treatment of ascites • Moderate sodium restriction (2 g or 90 mmol/day) and diuretics (spironolactone with or without furosemide) are the first-line treatment in patients with cirrhosis and grade 2 ascites. • After ascites is adequately mobilized, attempts should be made to taper the diuretics to the lowest dose necessary to maintain minimal or no ascites to prevent the development of adverse effects. • Fluid restriction is not necessary unless serum sodium is <125 mmol/L. • In patients receiving diuretics, body weight and serum creatinine and sodium should be regularly monitored to assess response and to detect the development of adverse effects. • Human albumin solution (20 to 40 g/week) or baclofen administration (10 mg/day, with a weekly increase of 10 mg/day, up to 30 mg/day) can be considered in cases of severe muscle cramps. • Large-volume paracentesis is the first-line treatment of grade 3 ascites. After paracentesis, sodium restriction and diuretics should be started. • Referral for liver transplant evaluation should be considered in patients with grade 2 or 3 ascites. • Nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers should be avoided in patients with cirrhosis and ascites. • Aminoglycosides should be avoided whenever possible in the treatment of bacterial infections. • For patients with cirrhosis and diuretic-responsive ascites, controversial data suggest potential benefits of long-term infusion of human albumin solution. At present, no recommendation can be made for its use in routine clinical practice.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the loop diuretics are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Loop Diuretics[3-7]

Indication	Bumetanide	Ethacrynic Acid	Furosemide	Torsemide
Edema				
Adjunctive therapy in acute pulmonary edema			✔ * (injection)	
Treatment of congestion due to fluid overload in adults with NYHA Class II/III chronic heart failure			✔ ^	
Treatment of edema associated with congestive heart failure, hepatic disease, and renal disease	✔ †	✔ ‡	✔ §	✔
Rapid onset of diuresis is desired (e.g., in acute pulmonary edema) or when gastrointestinal absorption is impaired or oral therapy is not practical				✔ (injection)
Short-term management of ascites due to malignancy, idiopathic edema, and lymphedema		✔		
Short-term management of hospitalized pediatric patients, other than infants, with congenital heart disease or nephrotic syndrome		✔		
Hypertension				
Treatment of hypertension			✔ ‖¶	✔ ‖

*The intravenous administration of furosemide is indicated when a rapid onset of diuresis is desired.
†If impaired gastrointestinal absorption is suspected or oral administration is not practical, bumetanide should be given by the intramuscular or intravenous route.
‡Treatment of edema when an agent with greater diuretic potential than those commonly employed is required.
§If impaired gastrointestinal absorption is suspected or oral administration is not practical, furosemide should be given by the intramuscular or intravenous route.
‖Alone or in combination with other antihypertensive agents.
¶If impaired gastrointestinal absorption is suspected or oral administration is not practical, furosemide should be given by the intramuscular or intravenous route.
^Furoscix® for subcutaneous use. Furoscix® is not indicated for emergency situations or in patients with acute pulmonary edema. The On-Body Infusor will deliver only an 80-mg dose. Not indicated for chronic use and should be replaced with oral diuretics as soon as practical.

IV. Pharmacokinetics

The pharmacokinetic parameters of the loop diuretics are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Loop Diuretics[8]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Bumetanide	80 to 95	90 to 99	Liver, partial (% not reported)	Bile (2) Feces (10 to 20) Renal (50 to 81)	1 to 1.5
Ethacrynic acid	100	90	Liver (% not reported)	Renal (66)	1 to 4
Furosemide	47 to 70	91 to 99	Liver (10)	Feces (7 to 9) Renal (60 to 90)	0.5 to 2
Torsemide	80 to 90	99	Liver (80)	Renal (69)	3 to 6

V. Drug Interactions

Major drug interactions with the loop diuretics are listed in Table 5.

Table 5. Major Drug Interactions with the Loop Diuretics[8]

Generic Name(s)	Interaction	Mechanism
Loop diuretics (bumetanide, ethacrynic acid, furosemide, torsemide)	Desmopressin	Concomitant use of desmopressin nasal spray and a loop diuretic is contraindicated due to an increased risk of severe hyponatremia.
Loop diuretics (bumetanide, ethacrynic acid, furosemide, torsemide)	Cisapride	Possible additive prolongation of the QT interval due to electrolyte loss increases the risk of life-threatening cardiac arrhythmias, including torsades de pointes.
Loop diuretics (bumetanide, ethacrynic acid, furosemide)	Digitalis Glycosides	Diuretic-induced electrolyte disturbances may predispose patients to digitalis-induced arrhythmias.
Loop diuretics (ethacrynic acid, furosemide, torsemide)	Aminoglycosides	Auditory toxicity may be increased by possible synergistic activity. The mechanism is unknown.
Loop diuretics (bumetanide, ethacrynic acid, furosemide, torsemide)	Cisplatin	The combination of loop diuretics and cisplatin may cause additive ototoxicity through an unknown mechanism.
Loop diuretics (bumetanide, ethacrynic acid, furosemide, torsemide)	Lithium	Increased plasma lithium concentrations increase risk of toxicity. The mechanism is unknown.
Loop diuretics (bumetanide, ethacrynic acid, furosemide, torsemide)	Thiazide diuretics	The two classes of agents exhibit their diuretic action at different sites in the renal tubules and have synergistic effects that may result in profound diuresis and serious electrolyte abnormalities.
Loop diuretics (bumetanide, ethacrynic acid, furosemide, torsemide)	Dofetilide	Concurrent use of dofetilide and diuretics may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
Loop diuretics (bumetanide, ethacrynic acid, furosemide, torsemide)	Sotalol	Concurrent use of sotalol and diuretics may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
Loop diuretics (bumetanide)	Indomethacin	Concurrent use of bumetanide and indomethacin may result in reduced diuretic effectiveness and possible nephrotoxicity.

VI. Adverse Drug Events

The most common adverse drug events reported with the loop diuretics are listed in Table 6. The boxed warning for the loop diuretics is listed in Table 7.

Table 6. Adverse Drug Events (%) Reported with the Loop Diuretics[3-8]

Adverse Events	Bumetanide	Ethacrynic Acid	Furosemide	Torsemide
Cardiovascular				
Atrial Fibrillation	-	-	-	✔
Chest pain	<1	-	-	1
Edema	-	-	-	1
Electrocardiogram changes	<1	-	-	2
Hypotension	<1	-	✔	✔
Hypovolemia	-	✔	-	✔
Myalgia	-	-	-	2
Orthostatic hypotension	<1	-	✔	✔

Adverse Events	Bumetanide	Ethacrynic Acid	Furosemide	Torsemide
Shunt thrombosis	-	-	-	✔
Syncope	-	-	-	✔
Ventricular tachycardia	-	-	-	✔
Central Nervous System				
Apprehension	-	✔	-	-
Asterixis	<1	-	-	-
Asthenia	-	-	✔	2
Confusion	-	✔	-	-
Dizziness	1	-	✔	3
Fatigue	<1	✔	-	✔
Headache	<1	✔	✔	7
Insomnia	-	-	-	1
Nervousness	-	-	-	1
Paresthesia	-	-	✔	-
Restlessness	-	-	✔	-
Vertigo	<1	✔	✔	-
Xanthopsia	-	-	✔	-
Dermatologic				
Erythema multiforme	-	-	✔	-
Exfoliative dermatitis	-	-	✔	-
Hives	<1	-	-	-
Itching	<1	-	-	-
Pruritus	<1	-	✔	✔
Rash	<1	✔	✔	✔
Photosensitivity	-	-	✔	-
Purpura	-	-	✔	-
Scaling eczema	-	-	✔	-
Stevens-Johnson Syndrome	-	-	✔	-
Urticaria	-	-	✔	-
Endocrine and Metabolic				
Acute gout	-	✔	-	✔
Dehydration	<1	-	-	-
Electrolyte imbalance	-	-	✔	✔
Nipple tenderness	<1	-	-	-
Gastrointestinal				
Abdominal discomfort/pain	<1	✔	-	-
Anorexia	-	✔	✔	-
Constipation	-	-	✔	2
Diarrhea	<1	✔	✔	2
Dry mouth	<1	-	-	-
Dyspepsia	<1	-	✔	2
Dysphagia	-	✔	-	✔
Gastrointestinal bleed	-	✔	-	✔
Loss of appetite	-	-	✔	-
Malaise	-	✔	-	-
Nausea	<1	✔	✔	2
Pancreatitis	-	✔	✔	-
Polydipsia	-	-	-	✔
Vomiting	<1	✔	✔	✔
Genitourinary				
Difficulty maintaining an erection	<1	-	-	-
Premature ejaculation	<1	-	-	-
Hematologic				

Adverse Events	Bumetanide	Ethacrynic Acid	Furosemide	Torsemide
Agranulocytosis	-	✔	✔	-
Anemia	-	-	✔	-
Aplastic anemia	-	-	✔	-
Deviations in differential counts	<1	-	-	-
Deviations in hematocrit	<1	-	-	-
Deviations in hemoglobin	<1	-	-	-
Deviations in prothrombin time	<1	-	-	-
Deviations in white blood cell count	<1	-	-	-
Hemolytic anemia	-	-	✔	-
Henoch-Schönlein purpura	-	✔	-	-
Leukopenia	-	-	✔	-
Neutropenia	-	✔	-	-
Thrombocytopenia	<1	✔	✔	-
Hepatic				
Abnormal liver enzymes	✔	✔	-	-
Encephalopathy	<1	-	-	-
Jaundice	-	✔	✔	-
Laboratory Test Abnormalities				
Azotemia	11	-	-	-
Changes in alkaline phosphatase	<1	-	-	-
Changes in cholesterol	<1	-	-	-
Changes in serum proteins	<1	-	-	-
Changes in total serum bilirubin	<1	-	-	-
Hyperlipidemia	✔	✔	✔	✔
Hyperglycemia	7	✔	✔	✔
Hyperuricemia	18	✔	✔	✔
Hypernatremia	<1			
Hypocalcemia	✔	✔	✔	✔
Hypochloremia	15	-	-	-
Hypoglycemia	-	✔	-	-
Hypokalemia	15	✔	✔	✔
Hypomagnesemia	✔	✔	✔	✔
Hyponatremia	9	-	-	-
Serum creatinine increased	7	-	-	-
Variations in bicarbonate	3	-	-	-
Variations in calcium	2	-	-	-
Variation in CO_2 content	4	-	-	-
Variations in phosphorus	5	-	-	-
Musculoskeletal				
Arthralgia	-	-	-	2
Arthritic pain	<1	-	-	✔
Muscle cramps	1	-	✔	✔
Musculoskeletal pain	<1	-	-	-
Spasticity	-	-	✔	-
Renal				
Changes in creatinine clearance	<1	-	-	-
Glycosuria	<1	-	✔	-
Hematuria	-	✔	-	-
Interstitial nephritis	-	-	✔	-
Polyuria	-	-	-	7
Proteinuria	<1	-	-	-
Renal Failure	<1	-	-	-
Respiratory				

Adverse Events	Bumetanide	Ethacrynic Acid	Furosemide	Torsemide
Cough	-	-	-	2
Hyperventilation	<1	-	-	-
Rhinitis	-	-	-	3
Special Senses				
Blurred vision	-	✔	✔	-
Deafness	-	✔	-	-
Ear discomfort	<1	-	-	-
Fullness of ears	-	✔	-	-
Impaired hearing	<1	✔	✔	-
Ototoxicity	✔	✔	✔	✔
Tinnitus	-	✔	✔	-
Other				
Angioedema	-	-	-	✔
Chills	-	✔	-	-
Fever	-	✔	✔	-
Necrotizing angitis	-	-	✔	-
Systemic vasculitis	-	-	✔	-
Sore Throat	-	-	-	2
Sweating	<1	-	-	-
Thrombophlebitis	-	-	✔	-
Weakness	<1	-	✔	✔

✔ Percent not specified
- Event not reported

Table 7. Boxed Warning for Bumetanide and Furosemide[7]

WARNING
Loop diuretics are potent diuretics which, if given in excessive amounts, can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required and dose and dosage schedule have to be adjusted to the individual patient's needs.

VII. Dosing and Administration

The usual dosing regimens for the loop diuretics are listed in Table 8.

Table 8. Usual Dosing Regimens for the Loop Diuretics[3-8]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Bumetanide	Edema: Injection: 0.5 to 1 mg over one minute; maximum, 10 mg/day Tablet: 0.5 to 2 mg/day; maximum, 10 mg/day	Safety and efficacy in children have not been established.	Injection: 0.25 mg/mL Tablet: 0.5 mg 1 mg 2 mg
Ethacrynic acid	Edema: Tablet: 50 to 200 mg/day	Edema (13 months and older): Tablet: initial, 25 mg	Tablet: 25 mg
Furosemide	Congestion due to fluid overload in adults with NYHA Class II/III chronic heart failure: Kit: The single-use, on-body Infusor with prefilled cartridge is pre-programed to deliver 30 mg of furosemide over the	Edema: Injection: initial, 1 mg/kg; maintenance, may increase by 1 mg/kg not sooner than two hours after the previous dose; maximum,	Injection: 10 mg/mL Kit (subcutaneous): 80 mg/10 mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	first hour followed by 12.5 mg per hour for the subsequent 4 hours. Not for chronic use and should be replaced with oral diuretics as soon as practical Edema: Injection (acute pulmonary edema): 40 mg intravenously over 1 to 2 minutes; maintenance, may increase to 80 mg intravenously Injection: 20 to 40 mg as a single intravenous or intramuscular injection; maintenance, may repeat in two hours or increased by 20 mg until desired response Oral: 20 to 80 mg/days; maximum, 600 mg/day Hypertension: Injection, solution, tablet: 80 mg/day	6 mg/kg per dose Solution, tablet: 2 mg/kg as a single dose; maximum, 6 mg/kg per dose	Solution: 10 mg/ mL 40 mg/5 mL Tablet: 20 mg 40 mg 80 mg
Torsemide	Edema: Injection, tablet (chronic renal failure): initial, 20 mg once daily; maintenance, 200 mg/day Injection, tablet (congestive heart failure): initial, 10 to 20 mg once daily; maximum, 200 mg/day Injection, tablet (hepatic cirrhosis): initial, 5 to 10 mg once daily; maximum, 40 mg/day Hypertension: Injection, tablet: initial, 5 to 10 mg/day; maximum, 10 mg/day	Safety and efficacy in children have not been established.	Tablet: 5 mg 10 mg 20 mg 100 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the loop diuretics are summarized in Table 9.

Table 9. Comparative Clinical Trials with the Loop Diuretics

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cirrhosis				
Laffi et al.[22] (1991) Furosemide 25 mg/day vs torasemide* 10 mg/day	DB, RCT Nonazotemic cirrhotic patients with ascites	N=24 3 days	Primary: Percent increase in natriuresis, body weight loss, percent increase in diuresis, plasma aldosterone concentration, plasma renin activity Secondary: Not reported	Primary: Treatment with torasemide led to significantly greater natriuresis than furosemide (P<0.02). There was a greater percentage increase in basal values (day 1: 130 vs 50%; day 2: 104 vs 42%; and day 3: 65 vs 26%, respectively). Body weight loss was significantly higher with torasemide (2.5 kg) than with furosemide (1.3 kg; P<0.02). There was no significant difference (P=0.08) in the percent increase in diuresis among the treatment groups (day 1: 60 vs 26%; day 2: 35 vs 27%; day 3: 31 vs 24%). Plasma aldosterone concentrations (ng/mL) with torasemide were 0.79 and 0.94 at baseline and day three, respectively. Plasma aldosterone concentrations with furosemide were 0.54 and 0.52 at baseline and day three, respectively. Plasma renin activity (ng/mL/hr) with torasemide were 5.8 and 9.4 at baseline and day three, respectively. Plasma renin activity with furosemide were 4.2 and 5.4 at baseline and day three, respectively. Secondary: Not reported
Gerbes et al.[23] (1993) Furosemide 80 mg as a single dose vs	DB, RCT, XO Patients with cirrhosis and ascites	N=28 24 hours	Primary: Urine volume, urine sodium volume, urine potassium volume, plasma aldosterone concentration,	Primary: Treatment with torasemide led to greater cumulative 24 hour diuresis than furosemide (2,863 vs 2,111; P<0.05). There was no difference in cumulative 0 to 6 hour sodium excretion with torasemide or furosemide (95.7 vs 92.1 mmol, respectively; P value not significant). There was greater cumulative 6 to 24 hour sodium excretion

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
torasemide* 20 mg as a single dose			plasma renin activity Secondary: Not reported	with torasemide compared to furosemide (38.4 vs 16.6 mmol; P<0.05). There was no difference in cumulative 0 to 24 hour sodium excretion with torasemide or furosemide (134.0 vs 108.5 mmol, respectively; P value not significant). There was no difference in cumulative 0 to 6 hour potassium excretion with torasemide or furosemide (57.5 vs 39.9 mmol, respectively; P value not significant). There was greater cumulative 6 to 24 hour potassium excretion with torasemide compared to furosemide (36.0 vs 27.6 mmol; P<0.05). There was no difference in cumulative 0 to 24 hour potassium excretion with torasemide or furosemide (88.3 vs 68.0 mmol, respectively; P value not significant). Plasma aldosterone concentrations (ng/100 mL) with torasemide were 111.9 and 132 at baseline and 24 hours, respectively. Plasma aldosterone concentrations with furosemide were 105.7 and 131 at baseline and 24 hours, respectively. Plasma renin activity (ng/mL/hr) with torasemide were 29.9 and 30.6 at baseline and 24 hours, respectively. Plasma renin activity with furosemide were 34.7 and 36.8 at baseline and 24 hours, respectively. Secondary: Not reported
Fiaccadori et al.[24] (1993) Furosemide 50 mg/day vs torasemide* 20 mg/day Patients also received	DB, RCT Nonazotemic cirrhotic patients with controlled ascites	N=28 10 weeks	Primary: Excretion of phosphate, free water, sodium, potassium, calcium, and uric acid Secondary: Not reported	Primary: Furosemide produced more excretion of phosphates (P<0.001) and magnesium (P<0.05) compared to torasemide. Torasemide produced more excretion of free water (P<0.02). There was no difference in the excretion of sodium, potassium, calcium, or uric acid among the treatment groups. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
spironolactone 200 mg/day				
Abecasis et al.[25] (2001) Frusemide† 40 mg/day vs torsemide 20 mg/day Patients also received spironolactone 200 mg/day	OL, RCT Cirrhotic patients with ascites	N=46 11 to 12 days	Primary: Resolution of ascites, weight loss, diuretic dosage, diuretic response Secondary: Not reported	Primary: There was no difference in the percentages of patients with resolution of ascites with torsemide compared to frusemide (73 vs 75%; P value not significant). There was no difference in weight loss with torsemide compared to frusemide (8 vs 8.5 kg; P value not significant). More patients receiving frusemide required an increase in diuretic dosage (37.5%) than with torsemide (9%; P<0.05). Torsemide produced a greater diuretic response in 24 hours than frusemide (P<0.007).
Heart Failure/Edema				
Galløe et al.[26] (2006) Bumetanide 0.5 mg (0, 1, 2 or 4 tablets BID) plus trandolapril 0.5 mg (0, 1, 2 or 4 tablets QD) Treatment was combined to achieve 16 different dosage combinations.	DB, DD, RCT, multiple XO Patients with previous MI ≥3 years ago, had medical treatment for heart failure and ejection fraction between 0.36 and 0.54 estimated by echocardiography	N=16 14 days	Primary: Patient reported quality of life Secondary: Effects on kidney function, left ventricular function and blood pressure	Primary: Bumetanide 0.5 mg-treated patients experienced a 12% increase in well-being, but higher doses of bumetanide decreased patient's well-being by 12% compared to placebo (P<0.002). Increasing doses of bumetanide tended to increase tiredness (P=0.072). There were no significant effects of bumetanide therapy on the patients' opinion of their health, degree of dyspnea, appetite or work capacity. Secondary: Bumetanide therapy increased 24 hour urine production in a straight dose-dependent manner (P<0.0001), while trandolapril therapy had no effect (P=0.53). Bumetanide and trandolapril therapy did not alter the 24 hour creatinine excretion and creatinine clearance (P=0.33, P=0.11 and P=0.53, P=0.97, respectively). Bumetanide therapy decreased left ventricular function and increased heart rate in a dose-dependent manner (P<0.001). Left ventricular function was also nonsignificantly decreased with trandolapril therapy (P>0.062).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Trandolapril therapy significantly reduced SBP by maximally of 7.6 mm Hg (5.8%) with the lowest dose of 0.5 mg/day (P=0.007). Bumetanide therapy had no significant effect on DBP (P=0.23).
Hutcheon et al.[27] (1981) Bumetanide 1 to 2 mg/day vs furosemide 80 mg/day	DB, PG Patients with severe edema associated with CHF	N=20 3 days	Primary: Edema, symptoms of heart failure, safety and tolerability Secondary: Not reported	Primary: Each agent was effective in decreasing the edema and relieving the symptoms of heart failure. Side effects were not severe and were similar in both treatment groups. Muscle cramps and abdominal pain were deemed not severe. Electrolyte shifts indicative of hypochloremic alkalosis and hyponatremia were seen in two patients in the bumetanide group. Secondary: Not reported
Konecke et al.[28] (1981) Bumetanide vs furosemide No dose or frequency reported.	OL, PG, RCT Men and women with clinically detectable edema and signs and symptoms of CHF (e.g., rales, gallop rhythm, orthopnea, dyspnea, engorged neck veins, paroxysmal nocturnal dyspnea, congested liver, etc.)	N=42 6 months	Primary: Changes in weight, blood pressure, pulse, signs and symptoms of CHF, electrolytes and functional capacity, safety and tolerability Secondary: Not reported	Primary: There were no statistical differences in changes in body weight, blood pressure, edema, abdominal girth, and hepatomegaly and other signs and symptoms of CHF in patients receiving bumetanide vs furosemide. There were variable minor changes in serum sodium, potassium, chloride, and uric acid in both groups throughout the treatment. Changes remained within normal limits and reached significance for chloride at weeks eight and 16 in the bumetanide group. Functional capacity improved slightly or remained unchanged throughout treatment in both treatment groups. There were no major side effects that were medication related in both treatment groups. Secondary: Not reported
Nicholson et al.[29] (1977) Bumetanide 1 mg/day alternating	RCT, XO Patients with cirrhosis and fluid overload	N=10 6 months	Primary: Ascites and edema Secondary: Adverse events	Primary: Bumetanide and frusemide were both effective in controlling ascites and edema, with nine out of 10 patients showing a satisfactory response. Secondary:

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with 3 mg/day for 3 months vs frusemide† 40 mg/day alternating with 160 mg/day for 3 months				Side effects were reported in six patients. The most common side effects were urinary frequency and nocturia, which occurred in four patients taking bumetanide and 1 patient taking frusemide. There was one patient on bumetanide and one patient on frusemide who developed symptoms of postural hypotension.
Eshaghian et al.[30] (2006) Furosemide 0 to 40 mg/day (group 1) vs furosemide 41 to 80 mg/day (group 2) vs furosemide 81 to 160 mg/day (group 3) vs furosemide >160 mg/day (group 4)	Cohort Men and women with advanced systolic heart failure referred to a single university medical center for heart failure management and/or transplant evaluation from 1985 to 2004	N=1,354 2 years	Primary: All-cause mortality Secondary: Composite endpoint of death or urgent transplant	Primary: There were 269 deaths during the two year follow-up, with 182 deaths by year one and 87 deaths during year two. Of the 269 deaths, 91 deaths were due to progressive heart failure, 72 deaths were sudden, eight deaths were secondary to myocardial infarction and 101 were unknown. Survival estimates at one year were 91, 88, 80, and 69% for groups 1, 2, 3, and 4, respectively (P<0.0001). Survival estimates at two years were 83, 81, 68, and 53%, respectively (P<0.0001). Secondary: There were a total of 431 patients who received heart transplants by the end of the two year follow up: 223 urgent and 208 elective. The HRs for death from any cause, death and urgent transplantation, death from progressive heart failure, and sudden death for group 4 compared with group 1 were similar. On univariate analysis, compared with group 1, increasing loop diuretic dose were associated with a progressive increase in mortality (group 2: HR, 1.2; 95% CI, 0.8 to 1.7, group 3: HR, 2.1; 95% CI, 1.5 to 2.9, and group 4: HR, 3.4; 95% CI, 2.4 to 4.7).
Mentz et al.[31] (2016) ASCEND-HF Furosemide	Cohort analysis of ASCEND-HF (diuretic choice not randomized) Patients enrolled in	N=4,177	Primary: All-cause mortality or HF hospitalization through 30-days after discharge	Primary & Secondary: Of the 4,177 patients in the outcomes analysis cohort, 87% (n=3,620) received furosemide and 13% (n=557) received torsemide. Torsemide was associated with similar outcomes on unadjusted analysis (30-day mortality/HF hospitalization OR, 1.03; 95% CI, 0.73 to 1.45, P=0.88 and 180-day mortality HR, 0.97; 95% CI, 0.73 to 1.29; P=0.83). On inverse

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs torsemide	the ASCEND-HF Trial (patients with acute HF) discharged alive on either furosemide or torsemide		Secondary: 30-day all-cause mortality, 30-day HF hospitalization and 180-day all-cause mortality post-discharge	propensity weighted-adjusted analysis, torsemide use was associated with nominally lower 30-day mortality or HF hospitalization (OR, 0.89; 95% CI, 0.62 to 1.29; P=0.55), 30-day mortality (OR, 0.89; 95% CI, 0.40 to 1.97; P=0.78), 30-day HF hospitalization (OR, 0.87; 95% CI, 0.58 to 1.30; P=0.49) and 180-day mortality (HR, 0.86; 95% CI, 0.63 to 1.19; P=0.37) compared with furosemide.
Murray et al.[32] (2001) Furosemide vs torsemide	OL, RCT Patients with CHF	N=234 12 months	Primary: Readmission to the hospital for heart failure Secondary: Readmission for all cardiovascular causes and for all causes, numbers of hospital days, health-related quality of life	Primary: Patients receiving torsemide were less likely to need readmission for heart failure (32%) compared to furosemide (17%; P<0.01). Secondary: Patients receiving torsemide were less likely to need readmission for all cardiovascular causes (59%) compared to furosemide (44%; P=0.03). There was no difference in the rate of admissions for all causes among the treatment groups (76 vs 71%; P=0.36). Patients treated with torsemide had significantly fewer hospital days for heart failure (106 vs 296 days; P=0.02). Improvements in fatigue scores from baseline were significantly greater among patients treated with torsemide compared to furosemide at months 2, 8, and 12 (P<0.05).
Cosín et al.[33] (2002) Furosemide 40 mg/day orally or other diuretics vs torasemide* 10 mg/day orally	OL Patients with NYHA functional class II to III heart failure	N=1,377 12 months	Primary: Mortality, morbidity, functional class and serum potassium levels (<3.5 or >5 mEq/L) Secondary: Not reported	Primary: Total mortality was significantly lower in the torasemide group (2.2%) compared to the furosemide/other diuretics group (4.5%; P<0.05). Cardiac mortality was lower in patients receiving torasemide (1.4%) than in those receiving furosemide/other diuretics (3.5%; P<0.05). NYHA improvement in at least 1 class occurred in more patients who received torasemide (45.8%) than those who received furosemide/other diuretics (37.2%; P=0.00017). Abnormal potassium levels were observed in fewer torasemide patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(12.9%) than furosemide/other diuretics patients (17.9%; P=0.013).
Muller et al.[34] (2003) Furosemide vs torasemide*	R, OL Patients with NYHA functional class II-IV congestive heart failure	N=237 9 months	Primary: Clinical improvement in heart failure, quality of life, hospitalizations, safety and tolerability Secondary: Not reported	Primary: Clinical improvement in chronic heart failure was seen in both groups, but the trend to improve by at least one NYHA class was significant with torasemide (P=0.014) compared to furosemide-treated patients. There were no differences in adverse reactions and hospitalizations due to CHF. Secondary: Not reported
Kasama et al.[35] (2006) Furosemide 20 to 40 mg/day vs torasemide* 4 to 8 mg/day	RCT Patients with non-ischemic CHF (LVEF <45%) also being treated with an ACE inhibitor	N=40 6 months	Primary: Effect on cardiac sympathetic nerve activity (delayed heart to mediastinum count ratio, delayed total defect score, washout rate) Secondary: Effect on left ventricular remodeling (left ventricular end diastolic volume, left ventricular end systolic volume)	Primary: In the furosemide group at the end of treatment, mean heart to mediastinum count ratio increased from 1.68±0.18 to 1.71±0.19 (P value not significant), mean total defect score decreased from 42±11 to 40±12 (P value not significant), and mean washout rate decreased from 50±8% to 47±12% (P value not significant). In the torasemide group at the end of treatment, mean heart to mediastinum count ratio increased from 1.61±0.19 to 1.77±0.24 (P<0.001), mean total defect score decreased from 44±8 to 36±8 (P<0.001), and mean washout rate decreased from 52±12 to 41±14% (P=0.001). Secondary: In the furosemide group left ventricular end diastolic volume decreased from 174±24 to 165±34 mL (P value not significant), left ventricular end systolic volume decreased from 120±15 to 109±33 mL (P value not significant), and LVEF increased from 31±7 to 32±7% (P value not significant). In the torasemide group left ventricular end diastolic volume decreased from 173±22 to 147±30 mL (P<0.01), left ventricular end systolic volume decreased from 117±19 to 95±25 mL (P<0.001), and LVE increased from 31±7 to 34±7% (P value not significant).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Mentz et al.[36] (2023) TRANSFORM-HF Furosemide vs torasemide investigator-selected dosage	OL, pragmatic randomized trial Participants hospitalized with heart failure (regardless of ejection fraction) at 60 hospitals in the United States	N=2,859 30 months	Primary: All-cause mortality Secondary: Five secondary outcomes with all-cause mortality or all-cause hospitalization and total hospitalizations assessed over 12 months being highest in the hierarchy	Primary: Death occurred in 373 of 1431 patients (26.1%) in the torsemide group and 374 of 1428 patients (26.2%) in the furosemide group (hazard ratio, 1.02; 95% CI, 0.89 to 1.18). Secondary: Over 12 months following randomization, all-cause mortality or all-cause hospitalization occurred in 677 patients (47.3%) in the torsemide group and 704 patients (49.3%) in the furosemide group (hazard ratio, 0.92; 95% CI, 0.83 to 1.02). There were 940 total hospitalizations among 536 participants in the torsemide group and 987 total hospitalizations among 577 participants in the furosemide group (rate ratio, 0.94; 95% CI, 0.84 to 1.07). Results were similar across prespecified subgroups, including among patients with reduced, mildly reduced, or preserved ejection fraction.
Levy et al.[37] (1977) Furosemide 25 mg daily for 24 weeks vs spironolactone and HCTZ 25-25 mg/day (fixed-dose combination product) for 16 weeks following 8 weeks of furosemide monotherapy	DB, RCT Patients 27 to 79 years of age with arteriosclerotic heart disease, hypertensive heart disease, or rheumatic heart disease classes 1 to 3, and congestive heart failure requiring diuretic therapy	N=32 24 weeks	Primary: Change in heart failure symptoms, glucose, renin concentration, calcium, blood urea nitrogen, uric acid, creatinine, aldosterone, serum potassium level, adverse effects Secondary: Not reported	Primary: The combination therapy group and furosemide monotherapy group exhibited comparable control of heart failure symptoms. The combination therapy group was associated with a significant decrease in glucose and an increase in plasma renin concentration compared to furosemide monotherapy group (P<0.01). There were no significant differences in calcium, blood urea nitrogen, uric acid, or creatinine between the study groups. There was a significant increase in aldosterone secretion among patients randomized to the spironolactone and HCTZ group compared to the furosemide group (P<0.01). There was no significant difference in serum potassium level between treatment groups. No serious adverse effects were observed in either of the study groups. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Austin et al.[38] (1976) Furosemide 40 to 60 mg infused through a pulmonary artery catheter vs ethacrynic acid 25 to 50 mg infused through a pulmonary artery catheter	OS Men and women who underwent diagnostic right and transeptal left heart catheterization with chronic postcapillary pulmonary HTN with heart failure NYHA class II to IV	N=27 1 hour	Primary: Hemodynamic response (in the control state and at 20, 40, and 60 minutes after diuretic administration) including cardiac index, pulmonary artery, left atrial and systemic artery mean pressures, plasma volume, PBV and PEV Secondary: Not reported	Primary: The hemodynamic response with each medication was similar. When compared to control state, the reductions in pulmonary artery mean pressure at 20, 40, and 60 minutes after diuretic infusion with either ethacrynic acid or furosemide were significant (P<0.001). The average left atrial mean pressure also decreased from 22 mm Hg during the control period to 18 mm Hg at 20 minutes and to 15 mm Hg at 60 minutes post diuretic infusion (ethacrynic acid or furosemide; P<0.001). The mean cardiac index decreased significantly at 20, 40, and 60 minutes compared to the control state after diuretic infusion with either ethacrynic acid or furosemide (P<0.001). There was a significant decrease in plasma volume at 60 minutes post drug infusions (ethacrynic acid or furosemide; P<0.001). In contrast, there was no significant change in PBV, PEV, PEV/PBV, and systemic arterial pressure throughout the study period with ethacrynic acid or furosemide. Secondary: Not reported
Patterson et al.[39] (1994) Torsemide 5 mg QD vs torsemide 10 mg QD vs	DB, MC, PC, PG Men and women diagnosed with NYHA class II or III CHF and edema	N=66 7 days	Primary: Change in body weight from baseline Secondary: Change in urinary sodium, potassium, chloride excretion and urine volume after the first dose of drug	Primary: Patients receiving torsemide 10 and 20 mg had a significant decrease in weight (-1.62 and -1.30 kg, respectively) as compared to placebo. Torsemide 5 mg did not demonstrated a significant reduction in body weight compared to placebo (-0.60 kg). Secondary: Severity of edema decreased as the dose of torsemide increased. The adverse events did not increase with higher doses of torsemide.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
torsemide 20 mg QD vs placebo QD				
Senzaki et al.[40] (2008) Torasemide* (de novo group) vs torasemide* (replacement group) was converted from furosemide dosage using 0.2 mg torasemide* corresponding to 1 mg furosemide	RCT Pediatric patients (age range from 3 weeks to 17 years) with congested heart failure, patients newly diagnosed with CHF or previously treated with furosemide	N=102 3 to 4 weeks	Primary: Clinical signs and symptoms of congestive heart failure Secondary: Humoral factors, serum potassium levels, and adverse events	Primary The de novo torasemide group significantly improved the congestive heart failure index from 7.2±1.6 to 5.7±1.4 (P<0.05); however the replacement group did not. The replacement group baseline value of the congestive heart failure index was 7.4±2.4 and after treatment the mean value was 6.8±2.3. Secondary: The de novo and replacement groups significantly improved brain natriuretic peptide and aldosterone levels (P<0.05); however, plasma rennin activity was not significantly decreased among both groups. Serum potassium levels were significantly increased in the replacement group (P<0.05), but not in the de novo group. The most commonly reported adverse events of torasemide were those associated with loop diuretics in general.
Faris et al.[41] (2006) Loop diuretics (furosemide, bumetanide), thiazide diuretics (chlorothiazide), or potassium-sparing diuretics (amiloride, triamterene) vs	MA Adult patients with chronic heart failure	N=525 (14 trials) 2 to 52 weeks	Primary: Mortality Secondary: Effect of diuretic withdrawal on worsening of heart failure and exercise capacity	Primary: Mortality was reported in three of the seven placebo-controlled trials, and this analysis showed that mortality was lower for patients treated with diuretics than with placebo (3/111[2.7%] vs 12/110 [10.9%], respectively; OR, 0.24; 95% CI, 0.07 to 0.83; P=0.02). These results showed that patients treated with diuretics had an absolute risk reduction of 8% when compared to placebo and a number needed to treat of 12.5. Secondary: An analysis of pooled data from two trials showed lower admission rates for worsening heart failure in patients taking diuretics than in patients taking placebo (OR, 0.07; 95% CI, 0.01 to 0.52; P=0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo or active control (ACE inhibitors, digoxin)				Diuretics were found to improve exercise capacity, with a difference in means of 0.74 (95% CI, 0.37 to 1.11; P<0.0001) and of 0.67 (95% CI, 0.02 to 1.31; P=0.04.), respectively. The combined results of these 4 trials indicated that diuretics improved exercise capacity in participants with chronic heart failure with a difference in means of 0.72 (95% CI, 0.40 to 14; P<0.0001).
Hypertension				
Van der Heijden et al.[42] (1998) Bumetanide 1 mg/day for 6 weeks vs furosemide 40 mg/day for 6 weeks	DB, PC, XO Patients with HTN	N=27 24 weeks	Primary: Changes in blood pressure, serum lipid levels, lab values, safety and tolerability Secondary: Not reported	Primary: Bumetanide and furosemide reduced SBP by 8.2% (P<0.0002) and DBP by 4.5% (P<0.002). Overall SBP and DBP measurements were 12 and 4 mm Hg lower, respectively, when receiving bumetanide or furosemide vs placebo. Both furosemide and bumetanide increased TC by 5.0% (P<0.002), HDL-C by 1.7% (P value not significant), LDL-C by 4.8% (P<0.01), and TG by 12.4% (P<0.01). Serum glucose, magnesium, sodium, and potassium levels were unchanged in both treatment groups; whereas serum creatinine tended to increase (3.2%; P=0.09). Side effects were mild in severity with no discontinuation reported. In both bumetanide and furosemide treated patients, four patients reported hypertonic muscles, but was resolved within a couple of days. Secondary: Not reported
De Berrazueta et al.[43] (2007) Furosemide infused in 3 progressive solutions containing 475,	RCT Patients with HTN and healthy controls	N=59 Single dose	Primary: Dilatory effect on arteries and veins Secondary: Not reported	Primary: There were no significant changes in arterial dilation. Furosemide increased vasodilatation from 0.56±0.09 to 0.88±0.06 (P=0.000) in healthy control subjects and from 0.49±0.10 to 0.75±0.12 (P=0.000) in hypertensive patients. Torsemide increased venodilation from 0.46±0.06 to 0.70±0.11 (P=0.007) in control subjects and from 0.48±0.09 to 0.67±0.12 (P=0.03) in hypertensive patients.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
950, and 1,900 nmol/mL for arterial studies and 240, 480, and 960 nmol/mL for venous studies vs torasemide* infused in 3 solutions containing 400, 800, and 1,600 nmol/mL for arterial studies and 200, 400, and 800 nmol/mL for venous studies				Secondary: Not reported
von Dossow et al.[44] (2008) Furosemide 40 mg IV and 80 mg PO 2 hours after extubation on day 1 after surgery vs torasemide* 20 mg IV and 20 mg PO 2 hours after extubation on day 1 after surgery	DB, RCT Patients with secondary pulmonary HTN scheduled for elective valve replacement and/or coronary artery bypass graft	N=21 Day 1 after surgery	Primary: Cardiac output Secondary: Endothelin-1 and angiotensin-II	Primary: Cardiac output increased significantly (P=0.03) in the torasemide group compared to the furosemide group. Secondary: Endothelin-1 and angiotensin-II increased significantly (P=0.031) in the furosemide group compared to the torasemide group.
Vasavada et al.[45]	DB, RCT, two-	N=14	Primary:	Primary

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2003) Phase 1: Inpatient Furosemide 200 mg/day with sodium-free water (10 mL/kg) vs torsemide 100 mg/day with sodium-free water (10 mL/kg) Phase 2:Outpatient Furosemide 80 mg/day vs torsemide 40 mg/day	phase, XO Patients ≥18 years of age with chronic kidney disease (serum creatinine >1.4 mg/dL) and volume overload	3 weeks	Phase 1: Inpatient Change in 24-hour urinary sodium excretion Phase 2: Outpatient Primary: 24-hour ambulatory SBP Secondary: Potassium, calcium, protein excretion, diurnal variation of electrolyte and protein excretion, and glomerular filtration rate	Phase 1: Inpatient Furosemide and torsemide increased urinary sodium excretion from 199to 357 mEq/day and 213 to 398 mEq/day, respectively. These differences between the two diuretics were not statistically significant. Phase 2: Outpatient Both treatments had similar effects in reducing SBP (P=0.43). The SBP was reduced from baseline to post treatment by 9.7 mm Hg for torsemide (P=0.007) and 9.2 mm Hg for furosemide (P=0.021). Secondary: There were no significant differences in excretion rate profiles between torsemide and furosemide (P>0.17).
Pupita et al.[46] (1983) Furosemide 25 mg QD vs chlorthalidone 50 mg QD	RCT, XO Men and women with a mean age of 53.9±9.2 years with mild to moderate HTN	N=36 12 months	Primary: Blood pressure Secondary: Plasma electrolytes, adverse events	Primary: Patients taking chlorthalidone had significantly lower SBP at each monthly measurement compared to baseline (P<0.01). However, only DBP values at month five were significant compared to baseline (P<0.05). Patients taking furosemide had significantly lower SBP at months three, four, and five compared to baseline (P<0.05 for month three, and P<0.01 for months four and five). DBP values were significantly lower at all monthly measurements compared to baseline in patients taking furosemide (P<0.01). At month one, SBP decreased by 19.4 mm Hg with chlorthalidone and by 21.2 mm Hg with furosemide (P<0.001). DBP decreased by 11 mm Hg with chlorthalidone and by 12.6 mm Hg with furosemide at month one

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(P<0.001). Secondary: There were no significant changes in serum sodium levels with either chlorthalidone or furosemide. Patients taking chlorthalidone had significantly lower serum chloride levels compared to baseline at all points (P<0.01), whereas patients taking furosemide had significantly lower levels only at month six (P<0.05). Both chlorthalidone and furosemide significantly reduced serum potassium levels at all points compared to baseline (P<0.01). Patient taking chlorthalidone reported adverse effects including dizziness, transient abdominal disorder, and slight weakness. Patients taking furosemide reported transient early weakness and irritability. The rate of adverse events was not statistically significant in either treatment group.
Valmin K et al.[47] (1975) Furosemide 12.5, 25 or 40 mg BID vs HCTZ 12.5 mg BID vs placebo	DB, RCT, XO, 5 experimental periods each of 4 weeks Men and women with essential HTN	N=34 20 weeks	Primary: Blood pressure, urinary output, serum electrolytes, safety and tolerability Secondary: Not reported	Primary: When compared to placebo, there was a significant reduction of blood pressure with HCTZ 12.5 mg BID and furosemide 12.5 mg BID (P<0.05). Paired comparison showed that HCTZ 12.5 mg BID and furosemide 25 and 40 mg BID had a similar hypotensive effect, irrespective of the initial blood pressure (P>0.10). When compared to placebo, the urinary output increased significantly with furosemide 12.5, 25, or 40 mg BID (P<0.05, P<0.01 and P<0.001, respectively) but not with the HCTZ group (P>0.10). Sodium level did not alter during the various treatment periods when compared with the placebo period, or between the individual treatment periods (P>0.10). Potassium level fell significantly during the HCTZ period (P<0.001) and furosemide 25 mg and 40 mg BID period (P<0.01 and P<0.001, respectively). Potassium level was not significantly affected with furosemide 12.5 mg BID (P>0.10). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Araoye et al.[9] (1978) Furosemide 40 mg BID vs HCTZ 50 mg BID	DB, XO Patients with HTN	N=not specified 3 months	Primary: Blood Pressure Secondary: Not reported	Primary: Furosemide and HCTZ significantly reduced blood pressure. The decrease in blood pressure was consistently greater in the HCTZ group than with furosemide; however the difference was significant in regards to SBP only. Secondary: Not reported
Ogawa et al.[48] (2006) Furosemide 20 mg/day plus imidapril‡ 5 mg/day vs spironolactone 25 mg/day plus imidapril‡ 5 mg/day All patients were pre-treated with imidapril‡ for 1 year prior to trial onset.	PRO, RCT Adult patients with HTN and type 2 diabetes, with a urine albumin/ creatinine ratio >30 mg/g creatinine, and plasma BNP levels >100 pg/mL (suggestive of mild heart failure)	N=30 24 months	Primary: Change in BNP, urine albumin/ creatinine ratio, and blood pressure Secondary: Not reported	Primary: At 12 months, spironolactone-treated patients exhibited a significant reduction in BNP level from baseline compared to furosemide-treated patients (P<0.05). At 12 months, spironolactone-treated patients exhibited a significant reduction in urine albumin/creatinine ratio from baseline compared to furosemide-treated patients (P<0.05). Both treatments exhibited similar reductions in blood pressure from baseline (P value not reported). No adverse events were reported in this trial. Secondary: Not reported
Furumatsu et al.[49] (2008) Spironolactone 25 mg/day (triple blockade group)	MC, OL, PRO, RCT Patients 20 to 70 years of age, with controlled blood pressure <130/80	N=32 12 months	Primary: Reduction in proteinuria, urinary type IV collagen, SBP, DBP, mean blood pressure, creatinine,	Primary: At one year of therapy, patients randomized to the triple blockage group experienced a statistically significant 58% reduction in urinary protein level from baseline (P<0.05), while there was no difference in the control group. Compared to the control group, the triple blockade group experienced a significant reduction in proteinuria at one year of therapy (P<0.05).

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vs trichlormethiazide * 1 mg/day or furosemide 10 mg/day (control group) Study medications were added to ongoing therapy consisting of enalapril 5 mg/day and losartan 50 mg/day.	mm Hg, chronic nephropathy (defined by serum creatinine level <3 mg/dL or calculated creatinine concentration <30 mL/min), daily treatment with enalapril 5 mg and losartan 50 mg for at least 12 weeks, and persistent proteinuria (urinary protein excretion >0.5 g/day)		creatinine clearance, potassium, urinary aldosterone Secondary: Not reported	At one year of therapy, patients randomized to the triple blockage group experienced a statistically significant 40% reduction in urinary type IV collagen from baseline (P<0.05); while there was no difference in the control group. However there was no statistically significant difference in the change of urinary type IV collagen from baseline between the two study groups. There were no statistically significant differences between the two study groups in the following outcome measures: SBP, DBP, mean blood pressure, creatinine, creatinine clearance, potassium, and urinary aldosterone. Secondary: Not reported
Hannson et al.[50] (2000) NORDIL Conventional therapy (diuretic, β-blocker or both) vs diltiazem 180 to 360 mg QD	BE, MC, OL, PRO, RCT Patients 50 to 74 years of age with DBP ≥100 mm Hg and previously untreated	N=10,881 4.5 years	Primary: Combined fatal and nonfatal stroke, fatal and nonfatal MI, other cardiovascular death Secondary: Fatal plus nonfatal stroke and fatal plus nonfatal MI	Primary: The primary endpoint occurred in 403 of the diltiazem patients and 400 of the diuretic/β-blocker patients (RR, 1.00; 95% CI, 0.87 to 1.15; P=0.97). Secondary: Rates of secondary endpoints were similar between the groups. Fatal plus nonfatal stroke occurred in 159 of the diltiazem patients and 196 of the diuretic/β-blocker patients (P=0.04). Fatal plus nonfatal MI occurred in 183 of the diltiazem patients and 157 of the diuretic/β-blocker patients (P=0.17). Other endpoints were not statistically different between the groups including cardiovascular death (P=0.41), all cardiac events (P=0.57 and congestive heart failure (P=0.42).
Wiysonge et al.[51] (2007) Other antihypertensive therapies (i.e.,	MA 13 RCTs evaluating patients ≥18 years of age with HTN	N=91,561 Duration varied	Primary: All-cause mortality Secondary: Stroke, CHD, cardiovascular	Primary: There was not a significant difference observed in all-cause mortality between β-blocker therapy and placebo (RR, 0.99; 95% CI, 0.88 to 1.11; P value not reported), diuretics (RR, 1.04; 95% CI, 0.91 to 1.19; P value not reported) or renin-angiotensin system inhibitors (RR, 1.10; 95% CI, 0.98 to 1.24; P value not reported). There was a significantly higher rate in all-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo, diuretics, calcium channel blockers, or renin-angiotensin system inhibitors) vs β-blockers (atenolol, metoprolol, oxprenolol*, or propranolol)			death, total cardiovascular disease, adverse reactions	cause mortality with β-blocker therapy compared to calcium channel blockers (RR, 1.07; 95% CI, 1.00 to 1.14; P=0.04). Secondary: There was a significant decrease in stroke observed with β-blocker therapy compared to placebo (RR, 0.80; 95% CI, 0.66 to 0.96). Also there was a significant increase in stroke with β-blocker therapy compared to calcium channel blockers (RR, 1.24; 95% CI, 1.11 to 1.40) and renin-angiotensin system inhibitors (RR, 1.30; 95% CI, 1.11 to 1.53), but there was no difference observed compared to diuretics (RR, 1.17; 95% CI, 0.65 to 2.09). CHD risk was not significantly different between β-blocker therapy and placebo (RR, 0.93; 95% CI, 0.81 to 1.07]), diuretics (RR, 1.12; 95% CI, 0.82 to 1.54), calcium channel blockers (RR, 1.05; 95% CI, 0.96 to 1.15) or renin-angiotensin system inhibitors (RR, 0.90; 95% CI, 0.76 to 1.06). The risk of total cardiovascular disease was lower with β-blocker therapy compared to placebo (RR, 0.88; 95% CI, 0.79 to 0.97). The effect of β-blocker therapy on cardiovascular disease was significantly worse than that of calcium channel blockers (RR, 1.18; 95% CI, 1.08 to 1.29), but was not significantly different from that of diuretics (RR, 1.13; 95% CI, 0.99 to 1.28) or renin-angiotensin system inhibitors (RR, 1.00; 95% CI, 0.72 to 1.3). There was a significantly higher rate of discontinuation due to side effects with β-blocker therapy compared to diuretics (RR, 1.86; 95% CI, 1.39 to 2.50) and renin-angiotensin system inhibitors (RR, 1.41; 95% CI, 1.29 to 1.54), but there was no significant difference compared to calcium channel blockers (RR, 1.20; 95% CI, 0.71 to 2.04). Actual side effects were not reported.
Miscellaneous				
Bagshaw et al.[52] (2007) Loop diuretics (frusemide†,	MA Patients with acute renal failure	N=555 Variable duration	Primary: Mortality, need for renal replacement therapy, and renal recovery	Primary: There was no statistical difference in mortality between loop diuretics compared to placebo (OR, 1.28; 95% CI, 0.89 to 1.84; P=0.18). There was no statistical difference in renal recovery between loop

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
torasemide*) vs placebo			Secondary: Urine output, serum potassium level and acid-base status, duration of acute renal failure or renal replacement therapy, length of hospital stay, toxicity	diuretics and control (OR, 0.88; 95% CI, 0.59 to 1.31; P=0.5). Secondary: Loop diuretics were associated with a shorter duration of renal replacement therapy (weighted mean difference of 1.4 days; 95% CI, 0.2 to 2.3; P=0.02), shorter time to spontaneous decline in serum creatinine level (WMD, 2.1 days; 95% CI, 0.4 to 3.7; P=0.01), and a greater increase in urine output from baseline (OR, 2.6; 95% CI, 1.4 to 4.9; P=0.004). There was no data available on acid-base status, hospital status, hospital length of stay or health costs.
Galloe et al.[53] (2006) Bumetanide 0.5 mg (0, 1, 2, or 4 tablets BID) vs trandolapril 0.5 mg (0, 1, 2, or 4 tablets QD)	DB, PC, RCT, XO Men and women with previous MI ≥3 years ago, had medical treatment for heart failure and ejection fraction between 0.36 and 0.54 estimated by echo-cardiography (wall motion index)	N=16 14 days	Primary: Patient reported quality of life Secondary: Effects on the involved organs: kidney function, left ventricular function, blood pressure	Primary: Patient's well-being increased 12% with 0.5 mg bumetanide BID but higher doses bumetanide decreased patient's well-being by 12% compared to placebo (P<0.002). Increasing doses of bumetanide tended to increase tiredness (P=0.072). There were no statistically significant effects of bumetanide on the patient's opinion of their health, degree of dyspnea, appetite or work capacity. Secondary: Bumetanide increased 24-hour urine production in a straight dose-dependent manner (P<0.0001) while trandolapril had no effect (P=0.53). Bumetanide and trandolapril did not alter the 24-hour creatinine excretion and creatinine clearance (P=0.33, P=0.11 and P=0.53, P=0.97, respectively). Bumetanide decreased left ventricular function and increased heart rate in a dose dependent manner (P<0.001). Left ventricular function was also decreased with trandolapril but did not reach statistically significant. (P>0.062). Trandolapril significantly reduced SBP by maximally of 7.6 mm Hg (5.8%) with the lowest dose of 0.5 mg/day (P=0.007). Bumetanide had no significant effect on DBP (P=0.23).

*Synonym for torsemide.
†Synonym for furosemide.
‡Agent not available in the United States.

Drug regimen abbreviations: BID=twice daily, IV=intravenous, PO=oral, QD=once daily
Study design abbreviations: BE=blinded endpoint, DB=double blind, DD=double dummy, MA=meta analysis, MC=multicenter, OL=open label, OS=observational, PC=placebo controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, XO=cross over
Miscellaneous abbreviations: ACE inhibitor=angiotensin converting enzyme inhibitors, BNP=brain natriuretic peptide, CHD=coronary heart disease, CHF=congestive heart failure, CI=confidence interval, DBP=diastolic blood pressure, HCTZ=hydrochlorothiazide, HDL-C=high-density lipoprotein cholesterol, HTN=hypertension, HR=hazard ratio, LDL-C=low-density lipoprotein cholesterol, LVEF=left ventricular ejection fraction, MI=myocardial infarction, NYHA=New York Heart Association, PBV=pulmonary blood volume, PEV=pulmonary extravascular fluid volume, RR=relative risk, SBP=systolic blood pressure, TC=total cholesterol, TG=triglycerides

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 10. Relative Cost of the Loop Diuretics

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Bumetanide	injection, tablet	N/A	N/A	$$
Ethacrynic acid	tablet	Edecrin®*	$$$$$	$$$$$
Furosemide	injection, kit, solution, tablet	Furoscix®, Lasix®*	$$$	$
Torsemide	tablet	N/A	N/A	$

*Generic is available in at least one dosage form or strength.
N/A=Not available

X. Conclusions

All of the loop diuretics are approved for the treatment of edema associated with congestive heart failure, hepatic disease, or renal disease. Furosemide and torsemide are also approved for the treatment of hypertension. Additionally, ethacrynic acid is approved for the short-term treatment of ascites (due to malignancy, idiopathic edema, and lymphedema) and for the short-term treatment of hospitalized pediatric patients with congenital heart disease or the nephrotic syndrome.[3-7] All agents are available in a generic formulation.

Guidelines recommend the use of diuretics and sodium restriction for the management of ascites due to cirrhosis. Spironolactone is recommended as first-line therapy, either as monotherapy or in combination with furosemide.

Amiloride or eplerenone are alternative treatment options in patients experiencing gynecomastia with spironolactone.[21] Several studies have compared furosemide and torsemide in cirrhotic patients with ascites. Although torsemide significantly increased natriuresis and diuresis compared to furosemide, these effects were not consistently demonstrated across the studies. There was no difference in plasma renin or aldosterone concentrations among the treatment groups.[22-25]

For the treatment of chronic heart failure, guidelines recommend the use of diuretics in all patients who have evidence of volume overload. Loop diuretics are generally recommended as initial therapy in patients with left ventricular dysfunction. For those with persistent fluid retention despite treatment with a loop diuretic, a thiazide diuretic or metolazone may be added to the regimen. In patients with normal left ventricular function, either a thiazide diuretic or loop diuretic may be used as initial therapy to manage fluid overload.[10-11] There are relatively few studies that have directly compared the loop diuretics for the treatment of chronic heart failure. In open-label trials, torsemide decreased mortality, hospitalizations and improved NYHA functional class compared to treatment with furosemide. However, due to limitations in the study designs, it is difficult to draw firm conclusions about the results of these studies.[32-34]

There are several published guidelines on the treatment of hypertension. Thiazide-type diuretics are frequently recommended as initial therapy in patients with uncomplicated hypertension.[12-19] According to the National Heart, Lung, and Blood Institute's Eighth Report of The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8), thiazide-type diuretics should be utilized first-line for most patients with hypertension, either alone or in combination with another hypertensive from a different medication class (e.g., ACE inhibitors, ARBs, β-blockers, calcium channel blockers).[12] Several guidelines consistently recommend that the selection of an antihypertensive agent be based on compelling indications for use.[11-18] Most patients will require more than one antihypertensive medication to achieve blood pressure goals.[12-19]

In clinical trials, the thiazide diuretics have been shown to effectively lower blood pressure.[42-51] Some studies suggest that hydrochlorothiazide is more effective than a loop diuretic for lowering blood pressure.[9] However, a loop diuretic should be used when the glomerular filtration rate is <30 mL/min.[1,2]

Serious adverse events reported with the loop diuretics include electrolyte abnormalities, hypersensitivity reactions, and ototoxicity. Ethacrynic acid has a higher rate of ototoxicity than other loop diuretics and is less commonly used. Patients allergic to sulfonamides may also show hypersensitivity to bumetanide, furosemide, and torsemide. Ethacrynic acid is the only loop diuretic that is not a sulfonamide derivative and can be safely used in patients with a sulfonamide allergy.[3-8]

There is insufficient evidence to support that one brand loop diuretic is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand loop diuretics within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand loop diuretic is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Potassium-Sparing Diuretics
AHFS Class 402816
May 8, 2024

1. Overview

The potassium-sparing diuretics are approved for the treatment of congestive heart failure, edema, and hypertension.[1-3] They inhibit sodium-potassium ion exchange at the distal convoluted tubule, cortical collecting tubule, and collecting duct. This reduces both potassium and hydrogen secretion and their subsequent excretion.[1-5] When used alone, potassium-sparing diuretics have a weak diuretic and antihypertensive effect and increased risk of hyperkalemia.[2] The potassium-sparing diuretics are generally used in combination with other diuretics to help restore normal serum potassium levels or to prevent the development of hypokalemia.[1-2] Amiloride and triamterene are both available as a fixed-dose combination with hydrochlorothiazide. Hydrochlorothiazide inhibits the reabsorption of sodium and chloride in the cortical thick ascending limb of the loop of Henle and the early distal tubules. This action leads to an increase in the urinary excretion of sodium and chloride.[2-4]

The potassium-sparing diuretics that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All of the products are available in a generic formulation. This class was last reviewed in May 2022.

Table 1. Potassium-Sparing Diuretics Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Amiloride	tablet	N/A	amiloride
Triamterene	capsule	N/A	triamterene
Combination Products			
Amiloride and hydrochlorothiazide	tablet	N/A	amiloride and hydrochlorothiazide
Triamterene and hydrochlorothiazide	capsule, tablet	N/A	triamterene and hydrochlorothiazide

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List
N/A=Not available

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the potassium-sparing diuretics are summarized in Table 2.

Table 2. Treatment Guidelines Using the Potassium-Sparing Diuretics

Clinical Guideline	Recommendation(s)
American Heart Association/American College of Cardiology/ Heart Failure Society of America: **2022 AHA/ACC /HFSA Guideline for the Management of Heart Failure (2022)[5]**	<u>Treatment of Stage A heart failure (HF)</u> • Hypertension should be controlled in accordance with guideline-directed medication therapy for hypertension to prevent symptomatic HF. (LoE: A) • In patients with type 2 diabetes and either established CVD or at high cardiovascular risk, SGLT-2 inhibitors should be used to prevent hospitalizations for HF. (LoE: A) • In the general population, healthy lifestyle habits such as regular physical activity, maintaining normal weight, healthy dietary patterns, and avoiding smoking are helpful to reduce future risk of HF. (LoE: B) • Patients at risk of developing HF, natriuretic peptide biomarker-based screening followed by team-based care, including a cardiovascular specialist optimizing therapy, can be useful to prevent the development of LV dysfunction (systolic or diastolic) or new-onset HF. (LoE: B)

Clinical Guideline	Recommendation(s)
	Treatment of Stage B heart failure • In patients with LVEF≤40%, ACE inhibitors should be used to prevent HF and reduce mortality. (LoE: A) • In patients with a recent or remote history of MI or ACS, statins should be used to prevent symptomatic HF and adverse cardiovascular events. (LoE: A) • In patients with a recent MI and LVEF≤40% who are intolerant to ACE inhibitors, ARB should be used to prevent symptomatic HF and reduce mortality. (LoE: B) • In patients with a recent or remote history of MI or ACS and LVEF≤40%, evidence-based beta blockers should be used to reduce mortality. (LoE: B) • In patients who are at least 40 days post-MI with LVEF ≤30% and NYHA class I symptoms while receiving guideline-directed medication therapy and have reasonable expectation of meaningful survival for greater than one year, an implantable cardioverter-defibrillator is recommended for primary prevention of sudden cardiac death to reduce total mortality. (LoE: B) • In patients with LVEF ≤40%, beta blockers should be used to prevent symptomatic HF. (LoE: C) • In patients with LVEF ≤50%, thiazolidinediones should not be used because they increase the risk of HF, including hospitalizations. (LoE: B) • In patients with LVEF ≤50%, nondihydropyridine calcium channel blockers with negative inotropic effects may be harmful. (LoE: C) Treatment for Stage C Heart Failure with Reduced Ejection Fraction (HFrEF) • For patients with stage C HF, avoiding excessive sodium intake is reasonable to reduce congestive symptoms. (LoE: C) • In patients with HF who have fluid retention, diuretics are recommended to relieve congestion, improve symptoms, and prevent worsening HF. (LoE: B) • For patients with HF and congestive symptoms, addition of a thiazide (e.g., metolazone) to treatment with a loop diuretic should be reserved for patients who do not respond to moderate or high dose loop diuretics to minimize electrolyte abnormalities. (LoE: B) • In patients with HFrEF and NYHA class II to III symptoms, the use of an ARNI is recommended to reduce morbidity and mortality. (LoE: A) • In patients with previous or current symptoms of chronic HFrEF, the use of an ACE inhibitor is beneficial to reduce morbidity and mortality when the use of an ARNI is not feasible. (LoE: A) • In patients with previous or current symptoms of chronic HFrEF, who are intolerant to an ACE inhibitor because of cough or angioedema, and when the use of an ARNI is not feasible, the use of an ARB is recommended to reduce morbidity and mortality. (LoE: A) • In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality. (LoE: B) • ARNIs should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor. (LoE: B) • ARNI or ACE inhibitors should not be administered in patients with a history of angioedema. (LoE: C) • In patients with HFrEF, with current or previous symptoms, use of one of the three β-blockers proven to reduce mortality (e.g., bisoprolol, carvedilol, sustained-release metoprolol succinate) is recommended to reduce mortality and hospitalizations. (LoE: A) • In patients with HFrEF and NYHA class II to IV symptoms, a mineralocorticoid receptor antagonist (spironolactone or eplerenone) is recommended to reduce morbidity and mortality, if eGFR is >30 mL/min/1.73 m^2 and serum potassium

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	is <5.0 mEq/L. Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely followed thereafter to minimize risk of hyperkalemia and renal insufficiency. (LoE: A) • In patients taking a mineralocorticoid receptor antagonist whose serum potassium cannot be maintained at <5.5 mEq/L, mineralocorticoid receptor antagonist should be discontinued to avoid life threatening hyperkalemia. (LoE: B) • In patients with symptomatic chronic HFrEF, SGLT-2 an inhibitor is recommended to reduce hospitalization for HF and cardiovascular mortality, irrespective of the presence of type 2 diabetes. (LoE: A) • The combination of hydralazine and isosorbide dinitrate is recommended to improve symptoms and reduce morbidity and mortality for patients self-identified as African Americans with NYHA class III to IV HFrEF receiving optimal therapy. (LoE: A) • In patients with current or previous symptomatic HFrEF who cannot be given first-line agents, such as an ARNI, ACE inhibitor or ARB because of drug intolerance or renal insufficiency, a combination of hydralazine and isosorbide dinitrate might be considered to reduce morbidity and mortality. (LoE: C) • In patients with HF class II to IV symptoms, omega-3 polyunsaturated fatty acid supplementation may be reasonable to use as adjunctive therapy to reduce mortality and cardiovascular hospitalizations. (LoE: B) • In patients with chronic HFrEF without specific indication (e.g., venous thromboembolism, atrial fibrillation, a previous thromboembolic event, or a cardioembolic source, anticoagulation is not recommended. (LoE: B) • Dihydropyridine and non-dihydropyridine calcium channel blockers are not recommended for patients with HFrEF. (LoE: A) • In patients with HFrEF, vitamins, nutritional supplements, and hormonal therapy are not recommended other than to correct specific deficiencies. (LoE: B) • In patients with HFrEF, class IC antiarrhythmic medication and dronedarone may increase risk of mortality. (LoE: A) • In patients with HFrEF, thiazolidinediones increase the risk of worsening HF symptoms and hospitalizations. (LoE: A) • In patients with type 2 diabetes and high cardiovascular risk, the DPP-4 inhibitors, saxagliptin and alogliptin, increase the risk of HF hospitalization and should be avoided in patients with HF. (LoE: B) • In patients with HFrEF, nonsteroidal anti-inflammatory drugs worsen HF symptoms and should be avoided or withdrawn whenever possible. (LoE: B) • For patients with symptomatic (NYHA class II to III) stable chronic HFrEF (LVEF ≤35%) who are receiving guideline-directed medical therapy, including a maximally tolerated dose of a beta blocker, and who are in sinus rhythm with a heart rate of ≥70 beats per minute at rest, ivabradine can be beneficial to reduce HF hospitalizations and cardiovascular death. (LoE: B) • In patients with symptomatic HFrEF despite guideline-directed medical therapy or who are unable to tolerate guideline-directed medical therapy, digoxin might be considered to decrease hospitalizations for HF. (LoE: B) • In select high-risk patients with HFrEF and recent worsening of HF already on guideline-directed medical therapy, an oral soluble guanylate cyclase stimulator (vericiguat) may be considered to reduce HF hospitalization and cardiovascular death. (LoE: B) <u>Pharmacological treatment for Stage C HF with mildly reduced EF and improved EF</u> • In patients with HF with mildly reduced EF, SGLT-2 inhibitors can be beneficial in decreasing HF hospitalizations and cardiovascular mortality. (LoE: B)

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	• Among patients with current or previous symptomatic HF with mildly reduced EF (LVEF, 41 to 49%), use of evidence-based beta blockers for HFrEF, ARNI, ACE inhibitor or ARB, and mineralocorticoid receptor antagonists may be considered to reduce the risk of HF hospitalization and cardiovascular mortality, particularly among patients with LVEF on the lower end of this spectrum. (LoE: B) • In patients with HF with improved EF after treatment, guideline-directed medical therapy should be continued to prevent relapse of HF and LV dysfunction, even in patients who may become asymptomatic. (LoE: B) <u>Pharmacological treatment for Stage C HF with preserved EF (HFpEF)</u> • Patients with hypertension and HFpEF should have medication titrated to attain blood pressure targets in accordance with published clinical practice guidelines to prevent morbidity. (LoE: C) • SGLT-2 inhibitors can be beneficial in decreasing HF hospitalizations and cardiovascular mortality. (LoE: B) • In patients with HFpEF, the use of a mineralocorticoid receptor antagonist, ARB, or ARNI may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum. (LoE: B) • Routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or quality of life in patients with HFpEF is ineffective. (LoE: B) <u>Treatment of Stage D (advanced/refractory) HF</u> • For patients with advanced HF and hyponatremia, the benefit of fluid restriction to reduce congestive symptoms is uncertain. (LoE: C) • Continuous intravenous inotropic support is reasonable as "bridge therapy" in patients with HF (Stage D) refractory to guideline-directed medical therapy and device therapy who are eligible for and awaiting mechanical circulatory support or cardiac transplantation. (LoE: B) • In select patients with HF Stage D, despite optimal guideline-directed medical therapy and device therapy who are ineligible for either mechanical circulatory support or cardiac transplantation, continuous intravenous inotropic support may be considered as palliative therapy for symptom control and improvement in functional status. (LoE: B) • Long-term use of either continuous or intermittent, intravenous inotropic agents, for reasons other than palliative care or as a bridge to advanced therapies, is potentially harmful. (LoE: B)
European Society of Cardiology: **Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (2021)[6]**	<u>Pharmacological treatments indicated in patients with (NYHA Class II-IV) heart failure with reduced ejection fraction</u> • An ACE inhibitor is recommended, in addition to a β-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death. • A mineralocorticoid receptor antagonist (MRA) is recommended for patients with HFrEF, who remain symptomatic despite treatment with an ACE inhibitor and a β-blocker, to reduce the risk of HF hospitalization and death. • Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death. Dapagliflozin or empagliflozin are recommended, in addition to optimal medical therapy with an ACE-I/ARNI, a β-blocker and an MRA, for patients with HFrEF regardless of diabetes status. • Sacubitril-valsartan is recommended as a replacement for an ACE inhibitor to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE inhibitor, a β-blocker, and a mineralocorticoid receptor antagonist. • Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion. • Ivabradine should be considered to reduce the risk of HF hospitalization or

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	cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm despite treatment with an evidence-based dose of β-blocker (or maximum tolerated dose below that), ACE inhibitor (or ARB), and a mineralocorticoid receptor antagonist (or ARB). • Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm who are unable to tolerate or have contraindications for a β-blocker. Patients should also receive an ACE inhibitor (or ARB) and a mineralocorticoid receptor antagonist (or ARB). • An ARB is recommended to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients unable to tolerate an ACE inhibitor (patients should also receive a β-blocker and mineralocorticoid receptor antagonist). • An ARB may be considered to reduce the risk of HF hospitalization and death in patients who are symptomatic despite treatment with a β-blocker who are unable to tolerate a mineralocorticoid receptor antagonist. • Vericiguat may be considered in patients in NYHA class II-IV who have had worsening HF despite treatment with an ACE-I (or ARNI), a β-blocker and an MRA to reduce the risk of CV mortality or HF hospitalization. • Hydralazine and isosorbide dinitrate should be considered in self-identified black patients with LVEF ≤35% or with an LVEF <45% combined with a dilated LV in NYHA Class III–IV despite treatment with an ACE-I a β-blocker and a mineralocorticoid receptor antagonist to reduce the risk of HF hospitalization and death. • Hydralazine and isosorbide dinitrate may be considered in symptomatic patients with HFrEF who can tolerate neither an ACE inhibitor nor an ARB (or they are contraindicated) to reduce the risk of death. • Digoxin is a treatment with less-certain benefits and may be considered in symptomatic patients in sinus rhythm despite treatment with an ACE inhibitor (or ARB), a β-blocker and a mineralocorticoid receptor antagonist, to reduce the risk of hospitalization (both all-cause and HF-hospitalizations). <u>Recommendations for treatment of patients with (NYHA class II-IV) heart failure with mildly reduced ejection fraction (HFmrEF)</u> • Diuretics are recommended in patients with congestion and HFmrEF in order to alleviate symptoms and signs. • An ACE inhibitor may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • An ARB may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • A β-blocker may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • An MRA may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • Sacubitril/valsartan may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. <u>Recommendations for treatment of patients with heart failure with preserved ejection fraction (HFpEF)</u> • It is recommended to screen patients with HFpEF for both cardiovascular and noncardiovascular comorbidities, which, if present, should be treated provided safe and effective interventions exist to improve symptoms, well-being and/or prognosis. • Diuretics are recommended in congested patients with HFpEF in order to alleviate symptoms and signs.

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	<u>Recommendations for the primary prevention of heart failure in patients with risk factors for its development</u> • Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life. • Treatment with statins is recommended in patients at high risk of CV disease or with CV disease in order to prevent or delay the onset of HF, and to prevent HF hospitalizations. • SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with diabetes at high risk of CV disease or with CV disease in order to prevent HF hospitalizations. • Counselling against sedentary habit, obesity, cigarette smoking, and alcohol abuse is recommended to prevent or delay the onset of HF. <u>Recommendations for the initial management of patients with acute heart failure – pharmacotherapy</u> • Intravenous loop diuretics are recommended for all patients with acute HF admitted with signs/symptoms of fluid overload to improve symptoms. It is recommended to regularly monitor symptoms, urine output, renal function and electrolytes during use of intravenous diuretics. • Combination of a loop diuretic with thiazide type diuretic should be considered in patients with resistant oedema who do not respond to an increase in loop diuretic doses. • In patients with acute HF and SBP >110 mmHg, intravenous vasodilators may be considered as initial therapy to improve symptoms and reduce congestion. • Inotropic agents may be considered in patients with SBP <90 mmHg and evidence of hypoperfusion who do not respond to standard treatment, including fluid challenge, to improve peripheral perfusion and maintain end-organ function. • Inotropic agents are not recommended routinely, due to safety concerns, unless the patient has symptomatic hypotension and evidence of hypoperfusion. • A vasopressor, preferably norepinephrine, may be considered in patients with cardiogenic shock to increase blood pressure and vital organ perfusion. • Thromboembolism prophylaxis (e.g. with LMWH) is recommended in patients not already anticoagulated and with no contraindication to anticoagulation, to reduce the risk of deep venous thrombosis and pulmonary embolism. • Routine use of opiates is not recommended, unless in selected patients with severe/intractable pain or anxiety.
Eighth Joint National Committee (JNC 8): **2014 Evidence-based Guideline for the Management of High Blood Pressure in Adults (2014)**[7]	• Pharmacologic treatment should be initiated in patients ≥60 years of age to lower blood pressure at systolic blood pressure ≥150 mm Hg or diastolic blood pressure ≥90 mm Hg and to a goal systolic blood pressure <150 mm Hg and goal diastolic blood pressure <90 mm Hg. Adjustment of treatment is not necessary if treatment results in lower blood pressure and treatment is well tolerated and without adverse effects on health or quality of life. • In patients <60 years of age, pharmacologic treatment should be initiated to lower blood pressure at diastolic blood pressure ≥90 mm Hg to a goal diastolic blood pressure <90 mm Hg. • In patients <60 years of age, pharmacologic treatment should be initiated to lower blood pressure at systolic blood pressure ≥150 mm Hg to a goal diastolic blood pressure <140 mm Hg. • For patients ≥18 years of age with chronic kidney disease or diabetes, pharmacologic treatment should be initiated to lower blood pressure at systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg and to a goal systolic blood pressure <140 mm Hg and goal diastolic blood pressure <90 mm Hg.

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	• Initial antihypertensive treatment for the general nonblack population, including those with diabetes, should include thiazide-type diuretic, calcium channel blocker (CCB), ACE inhibitor, or ARB. • Initial antihypertensive treatment for the general black population, including those with diabetes, should include thiazide-type diuretic or CCB. • For patients ≥18 years of age with chronic kidney disease regardless of race or diabetes status, initial (or add-on) treatment should include an ACE inhibitor or ARB to improve kidney outcomes. • The main goal of antihypertensive treatment is to attain and maintain goal blood pressure. • If goal blood pressure is not attained within a month of treatment, the dose of the initial drug should be increased or second drug from the thiazide-type diuretic, CCB, ACE inhibitor, or ARB classes should be added. • If goal is not achieved with two drugs, a third drug from the thiazide-type diuretic, CCB, ACE inhibitor, or ARB classes should be added. • An ACE inhibitor and ARB should not be used together. • Antihypertensive classes can be used if the patient is unable to achieve goal blood pressure with three agents or had a contraindication to a preferred class. • If blood pressure is not able to be achieved or in complicated patients, referral to a hypertension specialist may be indicated.
International Society of Hypertension: **Global Hypertension Practice Guidelines (2020)[8]**	<u>Lifestyle modifications</u> • Lifestyle modification is the first line of antihypertensive treatment. • Salt reduction: Reduce salt added when preparing foods, and at the table. Avoid or limit consumption of high salt foods such as soy sauce, fast foods and processed food including breads and cereals high in salt. • Healthy diet: Eating a diet that is rich in whole grains, fruits, vegetables, polyunsaturated fats and dairy products and reducing food high in sugar, saturated fat and trans fats, such as the DASH diet. • Healthy drinks: Moderate consumption of coffee, green and black tea. Other beverages that can be beneficial include karkadé (hibiscus) tea, pomegranate juice, beetroot juice and cocoa. • Moderation of alcohol consumption: The recommended daily limit for alcohol consumptions is 2 standard drinks for men and 1.5 for women (10 g alcohol/standard drink). Avoid binge drinking. • Weight reduction: Body weight control is indicated to avoid obesity. Particularly abdominal obesity should be managed. Ethnic-specific cut-offs for BMI and waist circumference should be used. Alternatively, a waist-to-height ratio <0.5 is recommended for all populations. • Smoking cessation: Smoking is a major risk factor for cardiovascular disease (CVD), COPD and cancer. Smoking cessation and referral to smoking cessation programs are advised. • Regular physical activity: Studies suggest that regular aerobic and resistance exercise may be beneficial for both the prevention and treatment of hypertension. Moderate intensity aerobic exercise (walking, jogging, cycling, yoga, or swimming) for 30 minutes on five to seven days per week Strength training also can help reduce blood pressure. Performance of resistance/strength exercises on two to three days per week. • Reduce stress and induce mindfulness: Stress should be reduced and mindfulness or meditation introduced into the daily routine. • Reduce exposure to air pollution and cold temperature: Evidence from studies support a negative effect of air pollution on blood pressure in the long-term. <u>Pharmacological Treatment</u> • Ideal characteristics of drug treatment ○ Treatments should be evidence-based in relation to morbidity/mortality

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	prevention. o Use a once-daily regimen which provides 24-hour blood pressure control. o Treatment should be affordable and/or cost-effective relative to other agents. o Treatments should be well-tolerated. o Evidence of benefits of use of the medication in populations to which it is to be applied. • General scheme for drug treatment o Lifestyle modification is the first line of antihypertensive treatment. o Grade 1 hypertension (BP 140 to 159/ 90 to 99): Immediate drug treatment in high-risk patients or those with CVD, chronic kidney disease (CKD), diabetes mellitus (DM), or hypertension-mediated organ damage (HMOD). Drug treatment after three to six months of lifestyle intervention if BP still not controlled in low to moderate risk patients. o Grade 2 hypertension (BP ≥160/100): Immediate drug treatment in all patients. • Core drug-treatment strategy o Step 1: Dual low-dose combination (ACE inhibitor or ARB plus dihydropyridine-calcium channel blockers (DHP-CCB)); consider monotherapy in low-risk grade 1 hypertension or in very old (≥80 years) or frail patients; consider ACE/ARB plus thiazide-like diuretic in post-stroke, very elderly, incipient HF, or CCB intolerance; consider ACE/ARB plus DHP-CCB or DHP-CCB plus thiazide-like diuretics in black patients. o Step 2: Dual full-dose combination (ACE inhibitor or ARB plus DHP-CCB); consider monotherapy in low-risk grade 1 hypertension or in very old (≥80 years) or frail patients; consider ACE/ARB plus thiazide-like diuretic in post-stroke, very elderly, incipient HF, or CCB intolerance. o Step 3: Triple combination (ACE/ARB plus DHP-CCB plus thiazide-like diuretic). o Step 4, resistant hypertension: triple combination plus spironolactone or other drug, alternatives include amiloride, doxazosin, eplerenone, clonidine, or β-blocker. Caution with spironolactone or other potassium sparing diuretics when estimated GFR <45 mL/min/1.73m^2 or K+ >4.5 mmol/L. o Consider β-blockers at any treatment step when there is a specific indications for their use, e.g., heart failure, angina, post-MI, atrial fibrillation, or younger women planning pregnancy or pregnant.
Hypertension Canada: **2020 Guidelines for the Prevention, Diagnosis, Risk Assessment, and Treatment of Hypertension in Adults and Children (2020)[9]**	<u>Indications for drug therapy for adults with hypertension without compelling indications for specific agents</u> • Antihypertensive therapy should be prescribed for average diastolic blood pressure (DBP) measurements of ≥100 mmHg or average systolic blood pressure (SBP) measurements of ≥160 mmHg in patients without macrovascular target organ damage or other cardiovascular risk factors. • Antihypertensive therapy should be strongly considered for average DPB readings ≥90 mmHg or for average SBP readings ≥140 mmHg in the presence of macrovascular target organ damage or other independent cardiovascular risk factors. • For high-risk patients, aged 50 years or older, with SBP levels ≥130 mmHg, intensive management to target a SBP <120 mmHg should be considered. Patient selection for intensive management is recommended and caution should be taken in certain high-risk groups.

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	Indications for drug therapy for adults with diastolic and with or without systolic hypertension
	• Initial therapy should be with either monotherapy or single pill combination (SPC).
	  ○ Recommended monotherapy choices are:
	  ▪ A thiazide/thiazide-like diuretic, with longer-acting diuretics preferred;
	  ▪ A β-blocker (in patients <60 years of age);
	  ▪ An angiotensin-converting enzyme (ACE) inhibitor (in nonblack patients);
	  ▪ An angiotensin receptor blocker (ARB); or
	  ▪ A long-acting calcium channel blocker (CCB).
	  ○ Recommended SPC choices are those in which an ACE inhibitor is combined with a CCB, ARB with a CCB, or ACE inhibitor or ARB with a diuretic.
	  ○ Hypokalemia should be avoided in patients treated with thiazide/thiazide-like diuretic monotherapy.
	• Additional antihypertensive drugs should be used if target BP levels are not achieved with standard-dose monotherapy. Add-on drugs should be chosen from first-line choices. Useful choices include a thiazide/thiazide-like diuretic or CCB with either: ACE inhibitor, ARB, or β-blocker. Caution should be exercised in combining a nondihydropyridine CCB and a β-blocker. The combination of an ACE inhibitor and an ARB is not recommended.
	• If BP is still not controlled with a combination of two or more first-line agents, or there are adverse effects, other antihypertensive drugs may be added.
	• Possible reasons for poor response to therapy should be considered.
	• α-Blockers are not recommended as first-line agents for uncomplicated hypertension; β-blockers are not recommended as first-line therapy for uncomplicated hypertension in patients ≥60 years of age; and ACE inhibitors are not recommended as first-line therapy for uncomplicated hypertension in black patients. However, these agents may be used in patients with certain comorbid conditions or in combination therapy.
	
	Indications for drug therapy for adults with isolated systolic hypertension
	• Initial therapy should be single-agent therapy with a thiazide/thiazide-like diuretic, a long-acting dihydropyridine CCB, or an ARB. If there are adverse effects, another drug from this group should be substituted. Hypokalemia should be avoided in patients treated with thiazide/thiazide-like diuretic monotherapy.
	• Additional antihypertensive drugs should be used if target BP levels are not achieved with standard-dose monotherapy. Add-on drugs should be chosen from first-line options.
	• If BP is still not controlled with a combination of two or more first-line agents, or there are adverse effects, other classes of drugs (such as α-blockers, ACE inhibitors, centrally acting agents, or nondihydropyridine CCBs) may be combined or substituted.
	• Possible reasons for poor response to therapy should be considered.
	• α-Blockers are not recommended as first-line agents for uncomplicated isolated systolic hypertension; and β-blockers are not recommended as first-line therapy for isolated systolic hypertension in patients ≥60 years of age. However, both agents may be used in patients with certain comorbid conditions or in combination therapy.
	
	Guidelines for hypertensive patients with coronary artery disease (CAD)
	• For most hypertensive patients with CAD, an ACE inhibitor or ARB is recommended.

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	• For hypertensive patients with CAD, but without coexisting systolic heart failure, the combination of an ACE inhibitor and ARB is not recommended. • For high-risk hypertensive patients, when combination therapy is being used, choices should be individualized. The combination of an ACE inhibitor and a dihydropyridine CCB is preferable to an ACE inhibitor and a thiazide/thiazide-like diuretic in selected patients. • For patients with stable angina pectoris but without previous heart failure, myocardial infarction, or coronary artery bypass surgery, either a β-blocker or CCB can be used as initial therapy. • Short-acting nifedipine should not be used. • When decreasing SBP to target levels in patients with established CAD (especially if isolated systolic hypertension is present), be cautious when the DBP is ≤60 mmHg because of concerns that myocardial ischemia might be exacerbated, especially in patients with left ventricular hypertrophy (LVH). <u>Guidelines for patients with hypertension who have had a recent myocardial infarction</u> • Initial therapy should include a β-blocker as well as an ACE inhibitor. • An ARB can be used if the patient is intolerant of an ACE inhibitor. • CCBs may be used in patients after myocardial infarction when β-blockers are contraindicated or not effective. Nondihydropyridine CCBs should not be used when there is heart failure, evidenced by pulmonary congestion on examination or radiography. <u>Treatment of hypertension in association with heart failure</u> • In patients with systolic dysfunction (ejection fraction <40%), ACE inhibitors and β-blockers are recommended for initial therapy. Aldosterone antagonists (mineralocorticoid receptor antagonists) may be combined in treatment for patients with a recent cardiovascular hospitalization, acute myocardial infarction, elevated B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide level, or New York Heart Association (NYHA) Class II-IV symptoms. Careful monitoring for hyperkalemia is recommended when combining an aldosterone antagonist with ACE inhibitor or ARB treatment. Other diuretics are recommended as additional therapy if needed. Beyond considerations of BP control, doses of ACE inhibitors or ARBs should be titrated to those reported to be effective in trials unless adverse effects become manifest. • An ARB is recommended if ACE inhibitors are not tolerated. • A combination of hydralazine and isosorbide dinitrate is recommended if ACE inhibitors and ARBs are contraindicated or not tolerated. • For hypertensive patients whose BP is not controlled, an ARB may be combined with an ACE inhibitor and other antihypertensive drug treatment. Careful monitoring should be used if combining an ACE inhibitor and an ARB because of potential adverse effects such as hypotension, hyperkalemia, and worsening renal function. Additional therapies may also include dihydropyridine CCBs. • An angiotensin receptor-neprilysin inhibitor (ARNI) should be used in place of an ACE inhibitor or ARB for patients with HFrEF (<40%) who remain symptomatic despite treatment with appropriate dose of guideline directed HF therapy. Eligible patients must have a serum potassium <5.2 mmol/L, an eGFR ≤30 mL/min/1.73m^2 and close surveillance of serum potassium and creatinine. <u>Treatment of hypertension in association with stroke</u> • BP management in acute ischemic stroke (onset to 72 hours) ○ Please refer to Stroke Best Practice recommendations. • BP management after acute ischemic stroke

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	○ Strong consideration should be given to the initiation of antihypertensive therapy after the acute phase of a stroke or transient ischemic attack. ○ After the acute phase of a stroke, BP-lowering treatment is recommended to a target of consistently <140/90 mmHg. ○ Treatment with an ACE inhibitor and thiazide/thiazide-like diuretic combination is preferred. ○ For patients with stroke, the combination of an ACE inhibitor and ARB is not recommended. • BP management in hemorrhagic stroke (onset to 72 hours) ○ Please refer to Stroke Best Practice recommendations. <u>Treatment of hypertension in association with LVH</u> • Hypertensive patients with LVH should be treated with antihypertensive therapy to decrease the rate of subsequent cardiovascular events. • The choice of initial therapy can be influenced by the presence of LVH. Initial therapy can be drug treatment using ACE inhibitors, ARBs, long-acting CCBs, or thiazide/thiazide-like diuretics. Direct arterial vasodilators such as hydralazine or minoxidil should not be used. <u>Treatment of hypertension in association with nondiabetic chronic kidney disease</u> • Individualize BP targets in patients with chronic kidney disease. Consider intensive targets (SBP <120 mmHg) in appropriate patients. • For patients with hypertension and proteinuric chronic kidney disease (urinary protein >150 mg per 24 hours or albumin to creatinine ratio >30 mg/mmol), initial therapy should be an ACE inhibitor or an ARB if there is intolerance to ACE inhibitors. • In most cases, combination therapy with other antihypertensive agents might be needed to reach target BP levels. • The combination of an ACE inhibitor and ARB is not recommended for patients with nonproteinuric chronic kidney disease. <u>Treatment of hypertension in association with renovascular disease</u> • Patients with hypertension attributable to atherosclerotic renal artery stenosis should be primarily medically managed because renal angioplasty and stenting offers no benefit over optimal medical therapy alone. • Renal artery angioplasty and stenting for atherosclerotic hemodynamically significant renal artery stenosis could be considered for patients with uncontrolled hypertension resistant to maximally tolerated pharmacotherapy, progressive renal function loss, and acute pulmonary edema. • Patients with confirmed renal fibromuscular dysplasia (FMD) should be referred to a hypertension specialist. • Renal artery angioplasty without stenting is recommended for treatment of FMD-related renal artery stenosis. Stenting is not recommended unless needed because of a periprocedural dissection. Surgical revascularization should be considered in cases of complex lesions less amendable to angioplasty, stenosis associated with complex aneurysm, and restenosis despite two unsuccessful attempts of angioplasty. <u>Treatment of hypertension in association with diabetes mellitus</u> • Persons with diabetes mellitus should be treated to attain SBP of <130 mmHg and DBP of <80 mmHg. • For persons with cardiovascular or kidney disease, including microalbuminuria, or with cardiovascular risk factors in addition to diabetes and hypertension, an ACE inhibitor or an ARB is recommended as initial therapy. • For persons with diabetes and hypertension not included in other guidelines in

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	this section, appropriate choices include (in alphabetical order): ACE inhibitors, ARBs, dihydropyridine CCBs, and thiazide/thiazide-like diuretics. • If target BP levels are not achieved with standard-dose monotherapy, additional antihypertensive therapy should be used. For persons in whom combination therapy with an ACE inhibitor is being considered, a dihydropyridine CCB is preferable to a thiazide/thiazide-like diuretic. <u>Resistant hypertension</u> • Resistant hypertension is defined as BP above target despite three or more BP-lowering drugs at optimal doses preferably including a diuretic (and usually a renin-angiotensin-aldosterone system blocker and a CCB. • Accurate office and out-of-office BP measurement is essential. • Other reasons for apparent resistant hypertension should be eliminated before diagnosing true resistant hypertension, including nonadherence, white coat effect, and secondary hypertension. • Pharmacotherapy with the additional use of spironolactone, bisoprolol, doxazosin, amiloride, eplerenone, or clonidine with the baseline regimen decreases BP significantly, with the greatest BP-lowering shown with spironolactone. • Patients with resistant hypertension should be referred to providers with expertise in diagnosis and management of hypertension. <u>Hypertension and pediatrics</u> • BP should be measured regularly in children three years of age or older; the auscultatory method is the gold-standard at present. • Initial therapy should be monotherapy, with an ACE inhibitor or ARB (not first-line in black children), or a long-acting dihydropyridine CCB. • The treatment t goal is systolic and diastolic office BP and/or ABPM < 95th percentile or <90th percentile in children with risk factors or target organ damage. • Complex cases should be referred to an expert in pediatric hypertension. <u>Hypertension and pregnancy</u> • Up to 7% of pregnancies are complicated by a hypertensive disorder of pregnancy, and approximately 5% of women will have chronic hypertension when they become pregnant. • The prevalence of hypertension in pregnancy is expected to increase with women becoming pregnant later in their reproductive years and the increasing prevalence of cardiovascular comorbidities such as increased preconception body mass index and maternal diabetes. • The possibility of pregnancy should be considered when managing women with hypertension who are of reproductive age. • Preconception counselling should be offered to all women with hypertension who are considering pregnancy. • ACE inhibitor and ARB therapy should be avoided before conception and during pregnancy unless there is a compelling indication for their use (i.e., proteinuric kidney disease). • Hypertension during pregnancy can increase the risk of adverse maternal and fetal outcomes, including an increased risk of preeclampsia, placental abruption, prematurity, small for gestational age infants, stillbirth, and maternal renal and retinal injury, thus generally requires involvement of an interdisciplinary team including obstetrical care providers. • Antihypertensive therapy is recommended for average SBP measurements of ≥140 mmHg or DBP measurements of ≥90 mmHg in pregnant women with chronic hypertension, gestational hypertension, or preeclampsia. Initial

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	antihypertensive therapy should be monotherapy from the following first-line drugs: oral labetalol, oral methyldopa, long-acting oral nifedipine, or other oral b-blockers (acebutolol, metoprolol, pindolol, and propranolol). Other antihypertensive drugs can be considered as second-line drugs including: clonidine, hydralazine, and thiazide diuretics. • Women with severe hypertension with SBP ≥160 mmHg or DBP ≥110 mmHg in pregnancy or postpartum require urgent antihypertensive therapy because it is considered an obstetrical emergency. • Antihypertensive drugs used in breastfeeding women include: labetalol, methyldopa, long-acting nifedipine, enalapril, or captopril.
European Society of Hypertension: **2023 Guidelines for the management of arterial hypertension (2023)[10]**	General recommendations for antihypertensive drug treatment • BP lowering should be prioritized over the selection of specific antihypertensive drug classes because treatment benefit largely originates from BP reduction. • Five major drug classes including, ACE inhibitors, ARBs, β-blockers, CCBs, and Thiazide/Thiazide-like diuretics have effectively reduced blood pressure and cardiovascular events in randomized controlled trials. These drugs and their combinations are recommended as the basis of antihypertensive treatment strategies. • Initiation of therapy with a two-drug combination is recommended for most hypertensive patients. Preferred combinations should comprise a RAS blocker (either an ACE inhibitor or an ARB) with a CCB or thiazide/thiazide-like diuretic. Other combinations of the five major drug classes can be used. • Initiation with monotherapy can be considered in patients with: grade 1 hypertension and low-risk if BP is only marginally elevated (less than 150 mmHg SBP and 95 mmHg DBP) high-normal BP and very high cardiovascular risk, frailty and/or and advance age. • If BP is not controlled with the initial two-drug combination by using the maximum recommended and tolerated dose of the respective components, treatment should be increased to a three-drug combination, usually a RAS blocker plus CCB plus thiazide/thiazide-like diuretic. • If BP is not controlled with a three-drug combination by using the maximum recommended and tolerated dose of the respective components, it is recommended to extend treatment according to the recommendations for resistant hypertension. • The use of single pill combinations should be preferred at any treatment step (i.e. during initiation of therapy with a two-drug combination and at any other step of treatment). • β-blocker should be used at initiation of therapy or at any treatment step as guideline-directed medical therapy (e.g., heart failure with reduced ejection fraction, anti-ischemic therapy in chronic coronary syndromes, heart rate control in atrial fibrillation). • β-blockers can be considered in the presence of several other conditions in which their use can be favorable. • The combination of two RAS blockers is not recommended due to increased risk of adverse events, in particular AKI. True-resistant hypertension • In resistant hypertension, it is recommended to reinforce lifestyle measures. • Drugs that can be considered as additional therapy in patients with resistant hypertension are preferably spironolactone (or other MRA), or β-blocker or Alpha-1 blockers or centrally acting agents (clonidine), or amiloride. • Thiazide/thiazide-like diuretics are recommended in resistant hypertension if estimated eGFR is ≥30 mL/min/1.73m^2. • Loop diuretics may be considered in patients with an estimated eGFR < 45 mL/min/1.73m^2 and should be used if eGFR falls below 30 mL/min/1.73m^2.

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	• Chlorthalidone (12.5 to 25 mg once daily) could be used with or without a loop diuretic if eGFR is <30 mL/min/1.73m^2. • Renal deprivation can be considered as an additional treatment option in patients with resistant hypertension if eGFR is >40 mL/min/1.73m^2. • Patients with resistant hypertension should be followed very closely. Follow-up includes periodical ambulatory blood pressure monitoring and assessment of hypertension-mediated organ damage, particularly kidney function and serum potassium levels. Regular use of home blood pressure monitoring and monitoring of drug adherence are desirable.
National Institute for Health and Clinical Excellence: **Hypertension in adults: diagnosis and management (2019)**[11]	Choosing antihypertensive drug treatment (for people with or without type II diabetes) • Where possible, recommend treatment with drugs taken only once a day. • Prescribe non-proprietary drugs where these are appropriate and minimize cost. • Offer people with isolated systolic hypertension (systolic blood pressure ≥160 mmHg) the same treatment as people with both raised systolic and diastolic blood pressure. • Offer antihypertensive drug treatment to women of child-bearing potential with diagnosed hypertension in line with recommendations in this guideline. For women considering pregnancy or who are pregnant or breastfeeding, manage hypertension in line with the recommendations on Management of pregnancy with chronic hypertension and Breastfeeding in 'Hypertension in pregnancy'. • When choosing antihypertensive drug treatment for adults of black African or African-Caribbean family origin, consider an angiotensin II receptor blocker, in preference to an angiotensin-converting enzyme inhibitor. Step one treatment • Patients <55 years of age should be offered a step one antihypertensive with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). • Offer an ACE inhibitor or an ARB to adults starting step 1 antihypertensive treatment who have type II diabetes and are of any age or family origin or those aged <55 years but not of black African or African-Caribbean family origin. • If an ACE inhibitor is not tolerated, offer an ARB. • Do not combine an ACE inhibitor with an ARB for the treatment of hypertension. • Offer a calcium channel blocker (CCB) to adults starting step 1 antihypertensive treatment who are >55 years of age and do not have diabetes and are of black African or African-Caribbean family origin and do not have type II diabetes and of any age. • If a CCB is not suitable, for example because of edema or intolerance, or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic. • If diuretic treatment is to be initiated or changed, offer a thiazide‑like diuretic, such as indapamide in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide. • For adults with hypertension who are already receiving treatment with bendroflumethiazide or hydrochlorothiazide, who have stable, well-controlled blood pressure, continue with their treatment. Step two treatment • Before considering next step treatment for hypertension discuss with the person if they are taking their medicine as prescribed and support adherence in line with NICE's guideline on “Medicines adherence: involving patients decisions about prescribed medicines and supporting adherence”.

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	• If hypertension is not controlled with a step one treatment of an ACE inhibitor or ARB, offer choice of one of the following drugs in addition to the step one treatment: a CCB or a thiazide-like diuretic. • If hypertension is not controlled in adults taking step one treatment of a CCB, offer the choice of one of the following drugs in addition to the step one treatment: an ACE inhibitor or an ARB or a thiazide-like diuretic. • If hypertension is not controlled in adults of black African or African–Caribbean family origin who do not have type 2 diabetes taking step one treatment, consider an ARB, in preference to an ACE inhibitor, in addition to step one treatment. <u>Step three treatment</u> • Before considering step three treatment, review the person's medications to ensure they are being taken at the optimal doses and discuss adherence (see recommendation under step two). • If hypertension is not controlled in adults taking step two treatment, offer a combination of an ACE inhibitor or ARB and a CCB and a thiazide-like diuretic. <u>Step four treatment</u> • If hypertension is not controlled in adults taking the optimal tolerated doses of an ACE inhibitor or an ARB plus a CCB and a thiazide-like diuretic, regard them as having resistant hypertension. • Before considering further treatment for a person with resistant hypertension, confirm elevated clinic blood pressure measurements using ambulatory or home blood pressure recordings, assess for postural hypotension, and discuss adherence. • For people with confirmed resistant hypertension, consider adding a fourth antihypertensive drug as step four treatment or seeking specialist advice. • Consider further diuretic therapy with low-dose spironolactone for adults with resistant hypertension starting step four treatment who have a blood potassium level of 4.5 mmol/l or less. Use particular caution in people with a reduced estimated glomerular filtration rate because they have an increased risk of hyperkalemia. • When using further diuretic therapy for step four treatment of resistant hypertension, monitor blood sodium and potassium and renal function within one month of starting treatment and repeat as needed thereafter. • Consider an alpha-blocker or beta-blocker for adults with resistant hypertension starting step four treatment who have a blood potassium level of more than 4.5 mmol/l. • If blood pressure remains uncontrolled in people with resistant hypertension taking the optimal tolerated doses of four drugs, seek specialist advice.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in Blacks (2010)**[12]	• To attain and maintain blood pressure (BP) below target levels, multiple antihypertensive drugs will be required in most hypertensive blacks. • Use of two-drug combination therapy when SBP is >15 mm Hg and/or DBP is >10 mm Hg above goal levels is increasingly recommended as first-line therapy. • Two-drug regimens have generally contained a thiazide-type diuretic; however, the combination of a calcium channel blocker (CCB) with either an ACE inhibitor or an ARB has been shown equally efficacious in BP lowering but with demonstrated superiority (CCB+ACE) for hard clinical outcomes compared with the same ACE inhibitor plus a thiazide-type diuretic. • In secondary prevention patients, the combination therapy should include a drug(s) with the appropriate compelling indications. • Certain classes of antihypertensive medications, specifically diuretics and

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	CCBs, lower BP on average more than β-blockers and renin-angiotensin system (RAS) blockers in black patients when used as monotherapies. • In the absence of compelling indications, when BP is near goal levels, monotherapy with a diuretic or a CCB is preferred. • Lifestyle modifications should be initiated in all patients with hypertension, whether or not pharmacotherapy is planned. • ACE inhibitors or ARBs are recommended as alternative monotherapy options in the treatment of hypertension in blacks. The rationale for their lower tier monotherapy recommendation is because they have consistently achieved lesser average reductions in BP relative to that observed with monotherapy using either a diuretic or CCB.
Kidney Disease Improving Clinical Outcomes Group: **KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease (2021)**[13]	<u>Blood pressure measurement</u> • The Work Group recommends standardized office blood pressure (BP) measurement in preference to routine office BP measurements for the management of high BP in adults. • The Work Group suggests that out-of-office BP measurements with ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM) be used to complement standardized office BP readings for the management of high BP. <u>Lifestyle interventions for lowering BP in patients with chronic kidney disease (CKD) not receiving dialysis</u> • The Work Group suggests targeting a sodium intake <2 grams of sodium per day (or <90 mmol of sodium per day, or <5 grams of sodium chloride per day) in patients with high BP and CKD. • The Work Group suggests that patients with high BP and CKD be advised to undertake moderate-intensity physical activity for a cumulative duration of at least 150 minutes per week, or to a level compatible with their cardiovascular and physical tolerance. <u>BP management in patients with CKD, with or without diabetes, not receiving dialysis</u> • The Work Group suggests that adults with high BP and CKD be treated with a target systolic BP (SBP) of <120 mmHg, when tolerated, using standardized office BP measurement. • The Work Group recommends starting renin-angiotensin-system inhibitors (RASi) (angiotensin-converting enzyme inhibitor [ACEi] or angiotensin II receptor blocker [ARB]) for people with high BP, CKD, and severely increased albuminuria without diabetes. • The Work Group suggests starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately increased albuminuria without diabetes. • The Work Group recommends starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately-to-severely increased albuminuria with diabetes. • The Work Group recommends avoiding any combination of ACEi, ARB, and direct renin inhibitor (DRI) therapy in patients with CKD, with or without diabetes. <u>BP management in kidney transplant recipients</u> • Treat adult kidney transplant recipients with high BP to a target BP of <130 mmHg systolic and <80 mmHg diastolic using standardized office BP measurement. • The Work Group recommends that a dihydropyridine calcium channel blocker (CCB) or an ARB be used as the first-line antihypertensive agent in adult kidney transplant recipients. <u>BP management in children with CKD</u>

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	• The Work Group suggests that in children with CKD, 24-hour mean arterial pressure by ABPM should be lowered to <50th percentile for age, sex, and height.
American College of Cardiology/ American Heart Association Task Force: **Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults (2017)[14]**	<u>Initiation of Blood Pressure (BP) Treatment for Overall Cardiovascular Disease (CVD) Risk</u> • Use of BP-lowering medications is recommended for secondary prevention of recurrent CVD events in patients with clinical CVD and an average systolic blood pressure (SBP) ≥130 mmHg or an average diastolic blood pressure (DBP) of ≥80 mmHg and for primary prevention in adults with an estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk of ≥10% and an average SBP of ≥130 mmHg or an average ≥80 mmHg. • Use of BP-lowering medication is recommended for primary prevention of CVD in adults with no history of CVD and with an estimated 10-year ASCVD risk <10% and an SBP of ≥140 mmHg or a DBP of ≥90 mmHg. • Simultaneous use of an angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), and/or renin inhibitor is potentially harmful and is not recommended to treat adults with hypertension. • For adults with confirmed hypertension and known CVD or 10-year ASCVD risk of ≥10%, a BP target <130/80 mmHg is recommended. For adults with confirmed hypertension without additional markers of increased CVD risk, a BP target <130/80 mmHg may be reasonable. • For initiation of antihypertensive drug therapy, first-line agents include thiazide diuretics, calcium channel blockers (CCBs), and ACE inhibitors or ARBs. • Initiation of antihypertensive drug therapy with two first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended in adults with stage 2 hypertension and an average BP >20/10 mmHg above their BP target. • Initiation of antihypertensive drug therapy with a single antihypertensive drug is reasonable in adults with stage 1 hypertension and BP goal <130/80 mmHg with dosage titration and sequential addition of other agents to achieve the BP target. <u>Stable Ischemic Heart Disease (SIHD)</u> • In adults with SIHD and hypertension, a BP target <130/80 is recommended. • Adults with SIHD and hypertension (BP <u>≥</u>130/80 mmHg) should be treated with medications [e.g., guideline-directed medical therapy (GDMT) beta-blockers, ACE inhibitors, or ARBs] for compelling indications [e.g., previous myocardial infarction (MI), stable angina] as first-line therapy, with the addition of other drugs (e.g., dihydropyridine CCBs, thiazide diuretics, and/or mineralocorticoid receptor antagonists) as needed to further control hypertension. • In adults with SIHD with angina and persistent uncontrolled hypertension, the addition of dihydropyridine CCBs to GDMT beta-blockers is recommended. • In adults who have had a MI or acute coronary syndrome, it is reasonable to continue GDMT beta-blockers beyond three years as long-term therapy for hypertension. • Beta-blockers and/or CCBs might be considered to control hypertension in patients with coronary artery disease (CAD) had an MI more than three years ago and have angina. <u>Heart Failure</u> • In adults with increased risk of HF, the optimal BP in those with hypertension should be <130 mmHg. • Adults with HFrEF and hypertension should be prescribed GDMT titrated to attain a BP <130/80 mmHg. • Non-dihydropyridine CCBs are not recommended in the treatment of

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	hypertension in adults with HFrEF. • In adults with HFpEF who present with symptoms of volume overload, diuretics should be prescribed to control hypertension. • Adults with HFpEF and persistent hypertension after management of volume overload should be prescribed ACE inhibitors or ARBs and beta-blockers titrated to attain SBP <130 mmHg. <u>CKD</u> • Adults with hypertension and CKD should be treated to a BP goal <130/80 mmHg. • In adults with hypertension and CKD [stage 3 or higher or stage 1 or 2 with albuminuria (≥300 mg/d, or ≥300 mg/g albumin-to-creatinine ratio or the equivalent in the first morning void)], treatment with an ACE inhibitor is reasonable to slow kidney disease progression. Treatment with an ARB may be reasonable if an ACE inhibitor is not tolerated. • After kidney transplantation, it is reasonable to treat patients with hypertension to a BP goal <130/80 mmHg and with a CCB on the basis of improved glomerular filtration rate (GFR) and kidney survival. <u>Cerebrovascular Disease</u> • In adults with intracerebral hemorrhage (ICH) who present with SBP >220 mmHg, it is reasonable to use continuous intravenous (IV) drug infusion and close BP monitoring to lower levels. Immediate lowering of SBP to <140 mmHg in adults with spontaneous ICH who present within six hours of the acute event and have an SBP between 150 mmHg and 220 mmHg is not of benefit to reduce death or severe disability and can be potentially harmful. • Adults with acute ischemic stroke and elevated BP who are eligible for treatment with IV tissue plasminogen activator (tPA) should have their BP slowly lowered to <185/110 mmHg before thrombolytic therapy is initiated. • In adults with an acute ischemic stroke, BP should be <185/110 mmHg before administration of IV tPA and should be maintained below 180/105 mmHg for at least the first 24 hours after initiation drug therapy. • Starting or restarting antihypertensive therapy during hospitalization in patients with BP >140/90 mmHg who are neurologically stable is safe and reasonable to improve long-term BP control, unless contraindicated. • In patient with BP ≥220/120 mmHg who did not receive IV alteplase or endovascular treatment and have no comorbid conditions requiring acute antihypertensive treatment, the benefit of initiating or reinitiating treatment of hypertension within the first 48 to 72 hours is uncertain. It might be reasonable to lower BP by 15% during the first 24 hours after onset of stroke. In patients with BP <220/120 mmHg with the same conditions, initiating or reinitiating treatment of hypertension within the first 48 to 72 hours after an acute ischemic stroke is not effective to prevent death or dependency. • Adults with previously treated stroke or transient ischemic attack should be restarted on antihypertensive treatment after the first few days of the index event to reduce the risk of recurrent stroke and other vascular events. Treatment with a thiazide diuretic, ACE inhibitor, or ARB, or combination treatment consisting of a thiazide diuretic plus ACE inhibitor, is useful. • Adults not previously treated for hypertension who experienced a stroke or transient ischemic attack and have an established BP ≥140/90 mmHg should be prescribed antihypertensive treatment a few days after the index event to reduce the risk of recurrent stroke and other vascular event. • For adults who experience a stroke or transient ischemic attack, selection of specific drugs should be individualized on the basis of patient comorbidities and agent pharmacological class.

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	• For adults who experience a stroke or transient ischemic attack, a BP goal <130/80 mmHg may be reasonable. • For adults with a lacunar stroke, a target SBP goal <130 mmHg may be reasonable. • In adults previously untreated for hypertension who experience an ischemic stroke or transient ischemic attack and have an SBP <140 mmHg and a DBP <90 mmHg, the usefulness of initiating antihypertensive treatment is not well established. Peripheral Artery Disease (PAD) • Adults with hypertension and PAD should be treated similarly to patients with hypertension without PAD. Diabetes Mellitus (DM) • In adults with DM and hypertension, antihypertensive drug treatment should be initiated at a BP of ≥130/80 mmHg with a treatment goal <130/80 mmHg. • In adults with DM and hypertension, all first-line classes of antihypertensive agents (i.e., diuretics, ACE inhibitors, ARBs, and CCBs) are useful and effective. • In adults with DM and hypertension, ACE inhibitors or ARBs may be considered in the presence of albuminuria. Atrial Fibrillation, Valvular Heart Disease, and Aortic disease • Treatment of hypertension can be useful for prevention of recurrence of AF. • In adults with asymptomatic aortic stenosis, hypertension should be treated with pharmacotherapy, starting at a low dose and gradually titrating upward as needed. • In patients with chronic aortic insufficiency, treatment of systolic hypertension with agents that do not slow the heart rate (i.e., avoid beta-blockers) is reasonable. • Beta-blockers are recommended as the preferred antihypertensive agents in patients with hypertension and thoracic aortic disease. Racial and Ethnic Differences in Treatment • In black adults with hypertension but without HF or CKD, including those with DM, initial antihypertensive treatment should include a thiazide-type diuretic or CCB. Two or more antihypertensive medications are recommended to achieve a BP target <130/80 mmHg in most adults with hypertension, especially in black adults with hypertension. Pregnancy • Women with hypertension who become pregnant, or are planning to become pregnant, should be transitioned to methyldopa, nifedipine, and/or labetalol during pregnancy. • Women with hypertension who become pregnant should not be treated with ACE inhibitors, ARBs, or direct renin inhibitors. Older Persons • Treatment of hypertension with an SBP treatment goal <130 mmHg is recommended for noninstitutionalized ambulatory community-dwelling adults (≥65 years of age) with an average SBP of ≥130 mmHg. • For older adults (≥65 years of age) with hypertension and a higher burden of comorbidity and limited life expectancy, clinical judgment, patient preference, and a team-based approach to assess risk/benefit is reasonable for decisions regarding intensity of BP lowering and choice of antihypertensive drugs.

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	Hypertensive Crises • In adults with a hypertensive emergency, admission to an intensive care unit is recommended for continuous monitoring of BP and target organ damage and for parenteral administration of an appropriate agent. • For adults with a compelling condition (i.e., aortic dissection, severe pre-eclampsia or eclampsia, or pheochromocytoma crisis), SBP should be reduced to <140 mmHg during the first hour and to <120 mmHg in aortic dissection. • For adults without a compelling condition, SBP should be reduced by no more than 25% within the first hours; then, if stable, to 160/100 mmHg within the next two to six hours; and then cautiously to normal during the following 24 to 48 hours. Cognitive Decline and Dementia • In adults with hypertension, BP lowering is reasonable to prevent cognitive decline and dementia. Patients Undergoing Surgical Procedures • In patients with hypertension undergoing major surgery who have been on beta-blockers chronically, beta-blockers should be continued. • In patients with hypertension undergoing planned elective major surgery, it is reasonable to continue medical therapy for hypertension until surgery. • In patients with hypertension undergoing major surgery, discontinuation of ACE inhibitors or ARBs perioperatively may be considered. • In patients with planned elective major surgery and SBP ≥180 mmHg or DBP ≥110 mmHg, deferring surgery may be considered. • For patients undergoing surgery, abrupt pre-operative discontinuation of beta-blockers or clonidine is potentially harmful. • Beta-blockers should not be started on the day of surgery in beta-blocker-naïve patients. • Patients with intraoperative hypertension should be managed with IV medications until such time as oral medications can be resumed.
American Diabetes Association: **Standards of Medical Care in Diabetes (2023)**[15]	Hypertension/blood pressure control • Blood pressure should be measured at every routine visit. When possible, patients found to have elevated blood pressure (systolic blood pressure 120 to 129 mmHg and diastolic <80 mmHg) should have blood pressure confirmed using multiple readings, including measurements on a separate day, to diagnose hypertension. Patients with blood pressure ≥180/110 and cardiovascular disease could be diagnosed with hypertension at a single visit. • All hypertensive patients with diabetes should monitor their blood pressure at home. • For patients with diabetes and hypertension, blood pressure targets should be individualized through a shared decision-making process that addresses cardiovascular risk, potential adverse effects of antihypertensive medications, and patient preferences. • Individuals with diabetes and hypertension qualify for antihypertensive drug therapy when the blood pressure is persistently elevated ≥130/80 mmHg. The on-treatment target blood pressure goal is <130/80 mmHg, if it can be safely attained. • In pregnant patients with diabetes and preexisting hypertension, a blood pressure target of 110 to 135/85 is suggested in the interest of reducing the risk for accelerated maternal hypertension and minimizing impaired fetal growth. • For patients with blood pressure >120/80, lifestyle intervention consists of weight loss when indicated, a Dietary Approaches to Stop Hypertension (DASH)-style eating pattern including reducing sodium and increasing

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	potassium intake, moderation of alcohol intake, and increased physical activity. • Patients with confirmed office-based blood pressure ≥130/80 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of pharmacologic therapy to achieve blood pressure goals. • Patients with confirmed office-based blood pressure ≥160/100 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of two drugs or a single pill combination of drugs demonstrated to reduce cardiovascular events in patients with diabetes. • Treatment for hypertension should include drug classes demonstrated to reduce cardiovascular events in patients with diabetes (ACE inhibitors, angiotensin receptor blockers, thiazide-like diuretics, or dihydropyridine calcium channel blockers). ACE inhibitors or angiotensin receptor blockers are recommended first-line therapy for hypertension in people with diabetes and coronary artery disease. • Multiple-drug therapy is generally required to achieve blood pressure targets (but not a combination of ACE inhibitors and angiotensin receptor blockers). • An ACE inhibitor or angiotensin receptor blocker, at the maximum tolerated dose indicated for blood pressure treatment, is the recommended first-line treatment for hypertension in patients with diabetes and urinary albumin–to–creatinine ratio ≥300 mg/g creatinine or 30 to 299 mg/g creatinine. If one class is not tolerated, the other should be substituted. • For patients treated with an ACE inhibitor, angiotensin receptor blocker, or diuretic, serum creatinine/estimated glomerular filtration rate and serum potassium levels should be monitored at least annually. • Patients with hypertension who are not meeting blood pressure targets on three classes of antihypertensive medications (including a diuretic) should be considered for mineralocorticoid receptor antagonist therapy. <u>Chronic kidney disease</u> • At least once a year, assess urinary albumin (e.g., spot urinary albumin–to–creatinine ratio) and estimated glomerular filtration rate in patients with type 1 diabetes with duration of five or more years and in all patients with type 2 diabetes. • In people with established diabetic kidney disease, urinary albumin (e.g., spot urinary albumin-to-creatinine ratio) and estimated glomerular filtration rate should be monitored one to four times per year depending on the stage of the disease. Optimize glucose control to reduce the risk or slow the progression of chronic kidney disease (CKD). • For patients with type 2 diabetes and diabetic kidney disease, use of a sodium-glucose cotransporter 2 inhibitor in patients with an estimated glomerular filtration rate ≥20 mL/min/1.73 m^2 and urinary albumin ≥200 mg/g creatinine is recommended to reduce CKD progression and cardiovascular events. • For patients with type 2 diabetes and diabetic kidney disease, use of a sodium–glucose cotransporter 2 inhibitor is recommended to reduce chronic kidney disease progression and cardiovascular events in patients with an estimated glomerular filtration rate ≥20 mL/min/1.73 m^2 and urinary albumin ranging from normal to 200 mg/g creatinine. • In people with type 2 diabetes and diabetic kidney disease, consider use of sodium–glucose cotransporter 2 inhibitors (if estimated glomerular filtration rate is ≥20 mL/min/1.73 m^2), a glucagon-like peptide 1 agonist, or a nonsteroidal mineralocorticoid receptor antagonist (if estimated glomerular filtration rate is ≥25 mL/min/1.73 m^2) additionally for cardiovascular risk reduction. • In people with chronic kidney disease and albuminuria who are at increased risk for cardiovascular events or chronic kidney disease progression, a nonsteroidal

Clinical Guideline	Recommendation(s)
	mineralocorticoid receptor antagonist shown to be effective in clinical trials is recommended to reduce chronic kidney disease progression and cardiovascular events. • Optimize blood pressure control and reduce blood pressure variability to reduce the risk or slow the progression of CKD. • Do not discontinue renin-angiotensin system blockade for minor increases in serum creatinine (≤30%) in the absence of volume depletion. • For people with nondialysis-dependent stage 3 or higher CKD, dietary protein intake should be a maximum of 0.8 g/kg body weight per day (the recommended daily allowance). For patients on dialysis, higher levels of dietary protein intake should be considered, since protein energy wasting is a major problem in some dialysis patients. • In nonpregnant patients with diabetes and hypertension, either an ACE inhibitor or an angiotensin receptor blocker is recommended for those with modestly elevated urinary albumin–to–creatinine ratio (30 to 299 mg/g creatinine) and is strongly recommended for those with urinary albumin–to–creatinine ratio ≥300 mg/g creatinine and/or estimated glomerular filtration rate <60 mL/min/1.73 m^2. • Periodically monitor serum creatinine and potassium levels for the development of increased creatinine and hyperkalemia when ACE inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists are used, or hypokalemia when diuretics are used. • An ACE inhibitor or an angiotensin receptor blocker is not recommended for the primary prevention of CKD in patients with diabetes who have normal blood pressure, normal urinary albumin–to–creatinine ratio (<30 mg/g creatinine), and normal estimated glomerular filtration rate. • Patients should be referred for evaluation by a nephrologist if they have continuously increasing urinary albumin levels and/or continuously decreasing estimated glomerular filtration rate and an estimated glomerular filtration rate <30 mL/min/1.73 m^2. • Promptly refer to a nephrologist for uncertainty about the etiology of kidney disease, difficult management issues, and rapidly progressing kidney disease.

*Agent is not available in the United States

III. Indications

The Food and Drug Administration (FDA)-approved indications for the potassium-sparing diuretics are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Potassium-Sparing Diuretics[1-2]

Indication(s)	Single Entity Agents		Combination Products	
	Amiloride	Triamterene	Amiloride and HCTZ	Triamterene and HCTZ
Congestive Heart Failure (or Edema) and Hypertension				
Help restore normal serum potassium levels in patients who develop hypokalemia on the kaliuretic diuretic	✔ *			
Prevent development of hypokalemia in patients who would be exposed to particular risk if hypokalemia were to develop	✔ *			
Treatment of edema associated with congestive		✔ †		

Indication(s)	Single Entity Agents		Combination Products	
	Amiloride	Triamterene	Amiloride and HCTZ	Triamterene and HCTZ
heart failure, cirrhosis of the liver and the nephrotic syndrome; steroid-induced edema, idiopathic edema and edema due to secondary hyperaldosteronism				
Use in patients who develop hypokalemia when thiazide or other kaliuretic diuretics are used alone, or in whom maintenance of normal serum potassium levels is considered to be clinically important			✔ ‡	
Use in patients who develop hypokalemia on hydrochlorothiazide alone, or in whom require a thiazide diuretic and in whom the development of hypokalemia cannot be risked				✔ ‡

*As adjunctive treatment with thiazide diuretics or other kaliuretic-diuretic agents.
†May be used alone or with other diuretics, either for its added diuretic effect or its potassium-sparing potential.
‡The fixed combination drug is not indicated for the initial therapy of edema or hypertension except in individuals in whom the development of hypokalemia cannot be risked.
HCTZ=hydrochlorothiazide

IV. Pharmacokinetics

The pharmacokinetic parameters of the potassium-sparing diuretics are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Potassium-Sparing Diuretics[3]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Amiloride	30 to 90	Not significant (% not reported)	Not metabolized	Feces (40 to 50) Renal (50)	6 to 9
Triamterene	30 to 70	55 to 67	Liver (80)	Renal (21)	1.5 to 2.5
Combination Products					
Amiloride and HCTZ	30 to 90/60 to 80	Not significant (% not reported)/ 10	Not metabolized	Feces (40 to 50) Renal (50)/ Renal (>60)	6 to 9/ 10 to 12
Triamterene and HCTZ	30 to 70/60 to 80	55 to 67/40	Liver (80)/ not reported	Renal (21)/ Renal (>60)	1.5 to 2.5/ 10 to 12

HCTZ=hydrochlorothiazide

V. Drug Interactions

Major drug interactions with the potassium-sparing diuretics are listed in Table 5.

Table 5. Major Drug Interactions with the Potassium-Sparing Diuretics[3]

Generic Name(s)	Interaction	Mechanism
Potassium-sparing diuretics (amiloride, triamterene)	Aldosterone blockers	Aldosterone blockers and potassium-sparing diuretics may exert additive pharmacologic effects. Hyperkalemia with the potential for cardiac arrhythmias may result.
Potassium-sparing diuretics (amiloride, triamterene)	Potassium preparations	Use of potassium preparations and potassium-sparing diuretics may increase the risk of hyperkalemia. Cardiac arrhythmias or cardiac arrest may occur.
Potassium-sparing diuretics	ACE inhibitors	Hyperkalemia, possibly with cardiac arrhythmias or arrest may occur with the combination of amiloride and ACE

Generic Name(s)	Interaction	Mechanism
(amiloride, triamterene)		inhibitors. Decreased aldosterone activity by ACE inhibitors may function synergistically with potassium conservation by amiloride to produce substantial hyperkalemia.
Potassium-sparing diuretics (amiloride, triamterene)	Indomethacin and derivatives	The combination of indomethacin and derivatives and triamterene may cause a sudden onset of nephrotoxicity.
Potassium-sparing diuretics (amiloride)	ARBs	The risk of hyperkalemia may be increased when amiloride is co-administered with ARBs. Decreased aldosterone activity by ARBs may function synergistically with potassium conservation by amiloride to produce substantial hyperkalemia.
Thiazide diuretics (HCTZ)	Dofetilide	Thiazide diuretics increase potassium excretion. Hypokalemia may occur, increasing the risk of torsades de pointes.
Thiazide diuretics (HCTZ)	Lithium	Thiazide diuretics decrease the renal clearance of lithium which leads to increased serum lithium levels. Lithium toxicity has occurred.
Potassium-sparing diuretics (amiloride)	Aliskiren	Hyperkalemia risk may be increased when aliskiren is coadministered with potassium-sparing diuretics. Decreased aldosterone activity by aliskiren may function synergistically with potassium conservation leading to the development of hyperkalemia.
Potassium-sparing diuretics (amiloride)	Macrolide immuno-suppressants	Macrolide immunosuppressives and potassium-sparing diuretics may exert additive effects on potassium leading to hyperkalemia.
Thiazide diuretics (HCTZ)	Diazoxide	Hyperglycemia may occur with symptoms similar to diabetes. The mechanism is unknown.
Thiazide diuretics (HCTZ)	Digitalis glycosides	Diuretic-induced electrolyte disturbances may predispose the patient to digitalis-induced cardiac arrhythmias.

ACE inhibitor=angiotensin converting enzyme inhibitor, ARB=angiotensin II receptor blocker, HCTZ=hydrochlorothiazide

VI. Adverse Drug Events

The most common adverse drug events reported with the potassium-sparing diuretics are listed in Table 6. The boxed warnings are listed in Tables 7 through 9.

Table 6. Adverse Drug Events (%) Reported with the Potassium-Sparing Diuretics[1-3]

Adverse Events	Single Entity Agents		Combination Products	
	Amiloride	Triamterene	Amiloride and HCTZ	Triamterene and HCTZ
Cardiovascular				
Arrhythmia	≤1	-	≤1	✔
Bradycardia	-	-	-	1 to 10
Chest pain	≤1	-	≤1	-
Congestive heart failure	-	-	-	1 to 10
Edema	-	-	-	1 to 10
Hypotension	-	-	1 to 10	1 to 10
Orthostatic hypotension	≤1	-	1 to 10	1 to 10
Palpitations	≤1	-	≤1	-
Central Nervous System				
Dizziness	1 to 10	✔	1 to 10	1 to 10
Fatigue	1 to 10	✔	1 to 10	1 to 10
Headache	1 to 10	✔	1 to 10	1 to 10

Adverse Events	Single Entity Agents		Combination Products	
	Amiloride	Triamterene	Amiloride and HCTZ	Triamterene and HCTZ
Dermatological				
Alopecia	≤1	-	≤1	≤1
Erythema multiforme	-	-	≤1	≤1
Exfoliative dermatitis	-	-	≤1	≤1
Photosensitivity	-	✔	1 to 10	1 to 10
Rash	-	✔	-	1 to 10
Stevens-Johnson syndrome	-	-	<1	<1
Toxic epidermal necrolysis	-	-	<1	<1
Endocrine and Metabolic				
Dehydration	1 to 10	-	1 to 10	<1
Gynecomastia	1 to 10	-	1 to 10	<1
Metabolic acidosis	1 to 10	-	1 to 10	<1
Postmenopausal bleeding	-	-	-	<1
Gastrointestinal				
Abdominal pain	1 to 10	-	1 to 10	✔
Anorexia	-	-	1 to 10	1 to 10
Appetite changes	1 to 10	-	1 to 10	-
Constipation	1 to 10	-	1 to 10	1 to 10
Diarrhea	1 to 10	✔	1 to 10	✔
Dry Mouth		✔		
Epigastric distress	-	-	1 to 10	1 to 10
Flatulence	≤1	-	≤1	-
Gastrointestinal bleeding	≤1	-	≤1	-
Nausea	1 to 10	✔	1 to 10	1 to 10
Pancreatitis	-	-	<1	<1
Vomiting	1 to 10	✔	1 to 10	✔
Genitourinary				
Bladder spasms	≤1	-	≤1	-
Dysuria	≤1	-	≤1	-
Impotence	1 to 10	-	1 to 10	<1
Polyuria	≤1	-	≤1	-
Renal dysfunction	-	✔	≤1	≤1
Hematological				
Agranulocytosis	-	-	≤1	≤1
Aplastic anemia	-	-	≤1	≤1
Hemolytic anemia	-	-	<1	<1
Leukopenia	-	-	≤1	≤1
Megaloblastic anemia		✔		
Thrombocytopenia	-	✔	≤1	≤1
Laboratory Test Abnormalities				
Hypercalcemia	-	-	<1	<1
Hyperkalemia	<10	✔	-	-
Hypokalemia	-	✔	1 to 10	1 to 10
Hyponatremia	1 to 10	-	1 to 10	1 to 10
Musculoskeletal				
Muscle cramps	1 to 10	-	1 to 10	✔
Weakness	1 to 10	✔	1 to 10	✔
Renal				
Azotemia		✔		
Interstitial nephritis	-	-	<1	<1
Renal failure	-	✔	<1	<1
Respiratory				

Adverse Events	Single Entity Agents		Combination Products	
	Amiloride	Triamterene	Amiloride and HCTZ	Triamterene and HCTZ
Cough	1 to 10	-	1 to 10	-
Dyspnea	1 to 10	-	1 to 10	1 to 10
Eosinophilic pneumonitis	-	-	<1	<1
Respiratory distress	-	-	<1	<1
Other				
Allergic myocarditis	-	-	<1	<1
Allergic reactions	-	✔	<1	<1
Hepatic function impairment	-	✔	<1	<1
Increased intraocular pressure	≤1	-	≤1	-
Jaundice	≤1	✔	≤1	-
Tinnitus	≤1	-	≤1	-
Visual disturbance	-	-	≤1	≤1

✔ Percent not specified
- Event not reported

Table 7. Boxed Warning for Amiloride[2]

WARNING
Like other potassium-conserving agents, amiloride may cause hyperkalemia (serum potassium levels greater than 5.5 mEq per liter) which, if uncorrected, is potentially fatal. Hyperkalemia occurs commonly (about 10%) when amiloride is used without a kaliuretic diuretic. This incidence is greater in patients with renal impairment, diabetes mellitus (with or without recognized renal insufficiency), and in the elderly. When amiloride is used concomitantly with a thiazide diuretic in patients without these complications, the risk of hyperkalemia is reduced to about 1 to 2%. It is thus essential to monitor serum potassium levels carefully in any patient receiving amiloride, particularly when it is first introduced, at the time of diuretic dosage adjustments, and during any illness that could affect renal function.

Table 8. Boxed Warning for Triamterene-Hydrochlorothiazide[2]

WARNING
Abnormal elevation of serum potassium levels (at least 5.5 mEq/L) can occur with all potassium-sparing agents, including triamterene. Hyperkalemia is more likely to occur in patients with renal impairment and diabetes (even without evidence of renal impairment), and in elderly or severely ill patients. Because uncorrected hyperkalemia may be fatal, serum potassium levels must be monitored at frequent intervals especially in patients receiving triamterene, when dosages are changed, or with any illness that may influence renal function.

Table 9. Boxed Warning for Amiloride-Hydrochlorothaizide[2]

WARNING
Like other potassium-conserving diuretic combinations, amiloride and hydrochlorothiazide may cause hyperkalemia (serum potassium levels greater than 5.5 mEq per liter). In patients without renal impairment or diabetes mellitus, the risk of hyperkalemia with this combination product is about 1 to 2 percent. This risk is higher in patients with renal impairment or diabetes mellitus (even without recognized diabetic nephropathy). Since hyperkalemia, if uncorrected, is potentially fatal, it is essential to monitor serum potassium levels carefully in any patient receiving amiloride hydrochloride and hydrochlorothiazide, particularly when it is first introduced, at the time of dosage adjustments, and during any illness that could affect renal function.

VII. Dosing and Administration

The usual dosing regimens for the potassium-sparing diuretics are listed in Table 10.

Table 10. Usual Dosing Regimens for the Potassium-Sparing Diuretics[1-3]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Amiloride	Congestive heart failure (or edema) and hypertension: Tablet: initial, 5 mg daily; may increase to 10 mg daily if needed; maximum, 20 mg	Safety and efficacy in children have not been established.	Tablet: 5 mg
Triamterene	Treatment of edema: Capsule: initial, 100 mg twice daily; maximum, 300 mg	Safety and efficacy in children have not been established.	Capsule: 50 mg 100 mg
Combination Products			
Amiloride and HCTZ	Congestive heart failure (or edema) and hypertension: Tablet: initial, 5-50 mg once daily; maintenance, 5-50 to 10-100 mg once daily or in divided doses	Safety and efficacy in children have not been established.	Tablet: 5-50 mg
Triamterene and HCTZ	Congestive heart failure (or edema) and hypertension: Capsule, tablet: initial, 37.5-25 mg once daily; maintenance: 37.5-25 to 75-50 mg once daily	Safety and efficacy in children have not been established.	Capsule: 37.5-25 mg Tablet: 37.5-25 mg 75-50 mg

HCTZ=hydrochlorothiazide

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the potassium-sparing diuretics are summarized in Table 11.

Table 11. Comparative Clinical Trials with the Potassium-Sparing Diuretics

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Edema/Heart Failure				
Bayliss et al.[16] (1987) Amiloride 5 mg QD and furosemide 40 mg	OS Patients with heart failure, 22 to 75 years of age, referred with breathlessness on moderate exertion (NYHA class 2 to 3) who were not previously treated	N=12 1 month	Primary: Average weight, heart rate at rest and maximal exercise, maximal treadmill exercise time, plasma renin, plasma aldosterone, noradrenaline at rest and maximal exercise Secondary: Not reported	Primary: Average weight was significantly reduced during treatment from 72.4 to 68.5 kg (P=0.0003). Resting heart rate decreased from 89 to 75 bpm (P=0.03). There was no significant change during exercise. Maximal treadmill exercise time significantly increased from 9.1 to 17.6 minutes (P=0.007). Plasma concentrations of renin increased from 1.1 to 4.2 ng/mL/hr at rest and from 2.5 to 11.3 ng/mL/hr upon exercise (P<0.007). Plasma concentrations of aldosterone increased from 169 to 488 pmol/L at rest and from 223 to 737 pmol/L upon exercise (P<0.007). Plasma concentrations of noradrenaline were significantly reduced (decreased to within normal ranges) at rest following treatment (P=0.005) but remained abnormally high at maximal exercise following treatment. Secondary: Not reported
Rengo et al.[17] (1979) Amiloride 15 mg QD vs amiloride and	RCT Patients 35 to 60 years of age with liver cirrhosis and ascites or CHF	N=30 15 days	Primary: Body weight, 24 hour diuresis, serum sodium, serum potassium, sodium and potassium urinary loss	Primary: All treatment groups had a significant reduction in body weight from baseline (P<0.001 for all). Amiloride and HCTZ-treated patients achieved a significantly greater reduction compared to amiloride-treated patients (P<0.001). All treatment groups significantly differed from baseline in 24 hour diuresis (P<0.01). Amiloride and HCTZ- and HCTZ-treated patients achieved greater diuresis compared to amiloride-treated patients (P<0.001 for both).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
HCTZ 15-150 mg QD (fixed-dose combination product) vs HCTZ 150 mg QD			Secondary: Not reported	Serum sodium was reduced from baseline in all treatment groups. HCTZ-treated patients had a significantly greater reduction than amiloride- (P<0.01) and amiloride and HCTZ-treated patients (P<0.001). Sodium urinary loss was seen with all treatments at day two, amiloride and HCTZ therapy had maintained the loss at day five (P<0.001 for both). Serum potassium decreased in HCTZ-treated patients but increased in amiloride- and amiloride and HCTZ-treated patients. HCTZ-treated patients had a marked increase in potassium urinary loss (P<0.001). Secondary: Not reported
Cheitlin et al.[18] (1991) Amiloride 5 or 10 mg QD for 7 days, followed by placebo plus HCTZ 50 or 100 mg QD for 14 days vs placebo for 14 days, followed by amiloride 5 or 10 mg plus HCTZ 50 or 100 mg QD for the next 7 days	DB, PC, RCT, XO Patients with a history CHF and ≥1 episode of pulmonary edema (NYHA class 2 to 3) who were not previously treated	N=11 21 days	Primary: Hemodynamic changes at rest and exercise Secondary: Not reported	Primary: At rest, there were no significant differences between placebo- and amiloride-treated patients in right atrial pressure, pulmonary atrial pressure, heart rate, pulmonary artery wedge pressure, systemic arterial pressure, right ventricular stroke work index, left ventricular stroke work index, systemic vascular resistance, cardiac index or stroke volume index (P values not reported). During exercise, there were significant differences between placebo- and amiloride-treated patients at the 50-watt stage in right atrial pressure (15.0 vs 10.5 mm Hg), pulmonary artery wedge pressure (28.6 vs 22.1 mm Hg), pulmonary artery diastolic pressure (32.2 vs 21.6 mm Hg), mean pulmonary artery pressure (44.4 vs 38.9 mm Hg), left ventricular stroke work index (69.5 vs 77.9 g-m/m^2) and stroke volume index (44.9 vs 46.2 cc/beat/m^2), respectively (P values not reported). There were no significant differences between placebo and amiloride therapy during exercise in right ventricular stroke work index, heart rate, aortic pressure, cardiac index and total systemic vascular resistance (P values not reported). Secondary: Not reported
Ghosh et al.[19] (1987)	PG, RCT, SB	N=60	Primary: Body weight,	Primary: Body weight was reduced with both treatments (P values not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Amiloride and HCTZ 2.5-25 mg QD (fixed-dose combination product) vs triamterene and HCTZ 50-25 mg QD (fixed-dose combination product)	Elderly patients with stable, mild to moderate CHF	8 weeks	clinical score, biochemistry Secondary: Not reported	Both treatments resulted in improvements in clinical scores; 95 and 88% of the amiloride/HCTZ- and triamterene/HCTZ-treated patients showed an improvement in heart failure signs with no patient's symptoms becoming worse (P values were not reported). Eighty five and 84% of amiloride/HCTZ- and triamterene/HCTZ-treated patients showed an improvement in heart failure symptoms (P values were not reported). There were no significant differences in serum sodium, potassium or urea between the two treatments (P values were not reported). Secondary: Not reported
Kohvakka.[20] (1998) HCTZ 50 mg BID vs amiloride 5 mg BID plus HCTZ 50 mg BID vs triamterene 75 mg BID plus HCTZ 50 mg BID vs KCl 1,000 mg BID plus HCTZ 50 mg BID	RCT, XO Patients 41 to 69 years of age with CHF (NYHA class 2 to 3) who developed persistent hypokalemia on HCTZ alone	N=25 5 months	Primary: Changes in weight, blood pressure, serum sodium, serum potassium and total body potassium Secondary: Percentage with hypokalemia, median days until hypokalemia detection, serum magnesium	Primary: Weight loss was significant in amiloride plus HCTZ- and triamterene plus HCTZ-treated patients (P=0.05 for both), but not in KCl plus HCTZ-treated patients (P value not reported), compared to HCTZ-treated patients. No significant changes in blood pressure were observed (P values not reported). No differences in serum sodium were observed in amiloride plus HCTZ- or triamterene plus HCTZ-treated patients (P values not reported). Serum sodium levels were slightly higher in KCl plus HCTZ-patients compared to HCTZ-treated patients (P=0.01). Serum potassium was found to be significantly higher in all combination treated-patients compared to HCTZ-treated patients (P=0.01 for all comparisons). Total body potassium was significantly higher in amiloride plus HCTZ- and triamterene plus HCTZ-treated patients (P=0.05 for both), but not in KCl plus HCTZ-treated patients (P value not reported), compared to HCTZ-treated patients. Secondary: The percentages of patients that became hypokalemic were 39, 52 and 52% in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				amiloride plus HCTZ-, triamterene plus HCTZ- and KCl plus HCTZ-treated patients (P values not reported). The median days until hypokalemia detection were 114.0, 75.0 and 51.5 for amiloride plus HCTZ-, triamterene plus HCTZ- and KCl plus HCTZ-treated patients (P values not reported). Serum magnesium was maintained at a significantly higher rate in amiloride plus HCTZ- and triamterene plus HCTZ- patients compared to KCl plus HCTZ-treated patients (P values not reported).
Faris et al.[21] (2006) Potassium-sparing diuretics (amiloride, triamterene), loop diuretics (furosemide, bumetanide), or thiazide diuretics (chlorothiazide) vs placebo or active control (ACE inhibitors, digoxin)	MA (14 trials) Adult patients with chronic heart failure	N=525 2 to 52 weeks	Primary: Mortality Secondary: Effect of diuretic withdrawal on worsening of heart failure and exercise capacity	Primary: Pooled data from three PC trials (n=202) reporting on mortality revealed that mortality was lower for diuretic-treated patients compared to placebo-treated patients (2.7 vs 10.9%, respectively; OR, 0.24; 95% CI, 0.07 to 0.83; P=0.02). The difference represents an absolute risk reduction of 8% in mortality in diuretic-treated patients (NNT, 12.5). Secondary: Pooled data from two PC trials (n=169) reporting on the effect of diuretics on worsening heart failure revealed lower admission rates for worsening heart failure in diuretic-treated patients compared to placebo-treated patients (OR, 0.07; 95% CI, 0.01 to 0.52; P=0.01). Pooled data from two parallel RCTs (n=43) reporting on the effect of diuretics on exercise capacity revealed that diuretic therapy improved exercise capacity compared to active control (WMD, 0.74; 95% CI, 0.37 to 1.11; P<0.0001). Pooled data from two XO RCTs (n=48) revealed similar results (WMD, 0.67; 95% CI, 0.02 to 1.31; P=0.04). In total (n=91), diuretic therapy improved exercise capacity in patients with chronic heart failure (WMD, 0.72; 95% CI, 0.40 to 1.04; P<0.0001).
Hypertension				
Heran et al.[22] (2010) Potassium sparing diuretics (amiloride,	SR (6 RCTs) Patients with a baseline office SBP ≥140 mm Hg and/or DBP ≥90	N=496 3 to 12 weeks	Primary: Quantify the dose-related SBP and DBP lowering efficacy of potassium sparing	Primary: *Blood pressure lowering efficacy of potassium sparing diuretics as a second drug:* There was no effect on SBP (-0.03 mm Hg; 95% CI, -2.90 to 2.83) and DBP (-0.22 mm Hg; 95% CI, -2.01 to 1.57) when potassium sparing diuretics were initiated at a dose of half the recommended starting dose. Due to the lack of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
triamterene) Monotherapy vs placebo and as combination therapy with another antihypertensive drug class (ACE inhibitor, ARB, β-blocker, calcium channel blocker, centrally-acting drugs, diuretics and renin inhibitors)	mm Hg		diuretics Secondary: Variability of blood pressure, pulse pressure, heart rate, withdrawals due to adverse effects	data, an estimate of the effect of higher doses or whether there was a dose response effect could not be determined. Secondary: *Blood pressure lowering efficacy of potassium sparing diuretics as a second drug:* The limited data did not suggest any effect of potassium sparing on blood pressure variability. Analysis of six trials assessing amiloride and triamterene did not suggest any effect of potassium sparing diuretics on pulse pressure. Two trials provided heart rate data and did not suggest any effect of potassium sparing diuretics on heart rate. An analysis of withdrawals due to adverse effects during three to 12 weeks of treatment with potassium sparing diuretics was reported in five of trials. The overall estimate showed no significant effect of potassium sparing diuretics on this outcomes (RR, 0.53; 95% CI, 0.19 to 1.51).
Multicenter Diuretic Cooperative Study Group[23] (1981) Amiloride 5 mg QD vs amiloride and HCTZ 5-50 mg QD (fixed-dose combination product) vs	DB, MC, RCT Patients 21 to 69 years of age with mild to moderate essential HTN (supine DBP 95 to 115 mm Hg)	N=179 12 weeks	Primary: Change from baseline in average supine SBP and DBP Secondary: Heart rate, body weight, serum potassium	Primary: Baseline vs 12 week average supine blood pressure was 153/101 vs 139/93 for amiloride-, 160/100 vs 137/90 for amiloride and HCTZ- and 154/101 vs 134/89 mm Hg for HCTZ-treated patients. Reductions in supine blood pressure were significant with all treatments (P<0.01). The SBP reduction was significantly greater with amiloride and HCTZ-treated patients compared to amiloride-treated patients at all weeks and HCTZ-treated patients at four and eight weeks (P<0.05, both). Secondary: No significant changes from baseline in heart rate were observed in amiloride and HCTZ-treated patients (P values not reported). An increase in heart rate of 3.3 bpm was observed in these patients (P<0.05). Changes in body weight from baseline were -1.17 kg in amiloride and HCTZ-, -0.72 kg in HCTZ- and 0.045 kg in amiloride-treated patients (P<0.05, for amiloride plus HCTZ only).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
HCTZ 50 mg QD				Changes in serum potassium from baseline were 0.23 in amiloride- (P<0.01), -0.38 in amiloride and HCTZ- (P<0.01) and -0.59 mEq/L in HCTZ-treated patients (P<0.01). The change in HCTZ-treated patients was statistically greater than the change in the amiloride and HCTZ-treated patients (P<0.05). Twenty three, two and zero percent of HCTZ-, amiloride and HCTZ- and amiloride-treated patients experienced hypokalemia.
Salmela et al.[24] (1986) Amiloride 2.5 mg/day and HCTZ 25 mg/day vs HCTZ 25 mg/day daily	DB, MC, PG, RCT Adult patients with mild to moderate HTN	N=40 12 weeks	Primary: Changes in blood pressure Secondary: Not reported	Primary: At the end of the first treatment period (four weeks), mean supine SBP and DBP was 161 and 91 mm Hg in amiloride plus HCTZ-treated patients (P<0.01 and P<0.001, respectively). At the end of the first treatment period (four weeks), mean supine SBP and DBP was 165 and 96 mm Hg in HCTZ-treated patients (P<0.01 for both). At the end of the second treatment period (eight weeks), mean supine SBP and DBP was 154 and 86 mm Hg in amiloride plus HCTZ-treated patients (P<0.01 and P<0.001). At the end of the second treatment period (eight weeks), mean supine SBP and DBP was 155 and 90 mm Hg in HCTZ-treated patients (P<0.001 and P<0.001). There were no significant differences in blood pressure reduction between the two treatments (P value not reported). Secondary: Not reported
Hood et al.[25] (2007) SALT study Amiloride 20 mg/day vs amiloride 40	DB, RCT, XO Adult patients with seated blood pressure of 140/90 to 170/110 mm Hg, plasma renin of ≤12 mU/L, plasma aldosterone-renin	N=57 42 weeks	Primary: Change in blood pressure and plasma renin from baseline between spironolactone 100 mg/day and bendro-flumethiazide 5 mg/day	Primary: Spironolactone 100 mg/day- and bendroflumethiazide 5 mg/day-treated patients did not exhibit a significant difference in blood pressure reduction from baseline (P value not reported). Secondary: Spironolactone 50 mg/day-treated patients exhibited a significant decrease in blood pressure from baseline compared to bendroflumethiazide 2.5 mg/day-treated patients (P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day vs spironolactone 50 mg/day vs spironolactone 100 mg/day vs bendro-flumethiazide* 2.5 mg/day vs bendro-flumethiazide* 5 mg/day vs losartan 100 mg/day vs placebo	ratio >750, previous fall in SBP ≥20 mm Hg after 1 month of OL treatment with spironolactone 50 mg/day		Secondary: Change in blood pressure and plasma renin from baseline between amiloride and other diuretics and between lower and higher doses of each diuretic	Losartan 100 mg-treated patients exhibited a significant decrease in blood pressure from baseline compared to bendroflumethiazide 2.5 mg/day-treated patients (P<0.05). High-dose bendroflumethiazide- and amiloride-treated patients exhibited significantly greater reductions in blood pressure compared to the lower doses (P<0.05). Spironolactone-treated patients exhibited a four-fold increase in baseline renin level compared to a two-fold increase observed in bendroflumethiazide-treated patients (P=0.003).
Kohvakka et al.[26] (1979) Amiloride 5 mg QD	PC, RCT, XO Patients 41 to 70 years of age with uncomplicated	N=31 3 months	Primary: Changes in blood pressure, serum potassium, sodium, creatinine, urate	Primary: No significant changes in blood pressure were observed with any of the treatments (P values not reported). Mean serum potassium was reduced with all treatments except with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs triamterene 75 mg QD vs KCl 1,500 mg QD vs spironolactone 50 mg QD vs placebo All patients were also receiving HCTZ 50 mg QD.	HTN, previously treated with antihypertensive agents for 1 to 6 years		and total body potassium Secondary: Not reported	spironolactone. KCl supplementation was least effective in elevating serum potassium. Total body potassium remained constant throughout treatment (P values not reported). Serum sodium remained within normal limits with all treatments (P values not reported). There were no significant changes in mean serum creatinine with any of the treatments (P values not reported). Serum urate concentration increased significantly with all treatments, including HCTZ monotherapy (P values not reported). Secondary: Not reported
Larochelle et al.[27] (1985) Amiloride 5 mg/day and HCTZ 50 mg/day vs HCTZ 50 mg/day	DB, RCT Ambulant patients 18 to 70 years of age with essential HTN who after not being treated for ≥2 weeks prior to the trial had a supine DBP of 95 to 109 mm Hg and a serum potassium level of >3.5 mmol/L	N=266 8 weeks	Primary: Blood pressure, serum potassium concentration Secondary: Not reported	Primary: At eight weeks, there were no differences between the two treatments in the mean blood pressure reductions (P value not reported). During the eight weeks of treatment, the HCTZ plus amiloride-treated patients experienced a decrease in mean supine blood pressure (159/99 to 138/88 mm Hg) and serum potassium levels (4.23 to 3.91 mmol/L) (P values not reported). During the eight weeks of treatment, HCTZ-treated patients experienced a reduction in mean supine blood pressure (157/99 to 138/87 mm Hg) and serum potassium levels (4.16 to 3.69 mmol/L) (P values not reported). Hypokalemia occurred less frequently in HCTZ plus amiloride-treated patients compared to HCTZ-treated patients (14 and 29%, respectively; P=0.0026). However, the proportions of patients with a potassium level exceeding 4.5

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				mmol/L were similar (4.5 vs 3.9%, respectively; P value not reported). Secondary: Not reported
Dean et al.[28] (1984) Amiloride and HCTZ 5-50 mg QD (fixed-dose combination product) vs triamterene and HCTZ 50-25 mg QD (fixed-dose combination product)	RCT, SB, XO Patients with mild to moderate HTN (DBP 95 to 110 mm Hg)	N=20 8 weeks	Primary: Blood pressure, hypokalemia, hyperkalemia, renal function tests Secondary: Not reported	Primary: Both treatments produced a comparable effect on blood pressure. The baseline standing and lying blood pressure was 168/105 and 168/104 mm Hg, respectively. After eight weeks, amiloride and HCTZ-treated patients had a standing and lying blood pressure of 145/92 and 145/90 mm Hg, respectively (P values not reported). After eight weeks, triamterene and HCTZ-treated patients had a standing and lying blood pressure of 142/93 and 143/91 mm Hg, respectively (P values were not reported). There were no cases of hypokalemia or hyperkalemia and no renal function changes with either treatment (P values were not reported). Secondary: Not reported
Maxwell et al.[29] (1985) Amiloride and HCTZ 50-25 mg QD (fixed-dose combination product) vs triamterene and HCTZ 5-50 mg QD (fixed-dose combination product)	OL, PRO, RCT Patients with mild to moderate HTN, mean supine DBP <90 or >114 mm Hg at the end of a 3 week placebo, run-in phase	N=84 9 weeks	Primary: Mean blood pressure changes Secondary: Not reported	Primary: Seventy three (n=30) and 81% (n=35) of triamterene and HCTZ- and amiloride and HCTZ-treated patients were maintained on the initial dosage throughout the trial, with no significant differences between the two treatments (P value not reported). At week nine, mean SBP and DBP was 136.2 and 87.4 mm Hg in triamterene and HCTZ-treated patients (P value not reported). At week nine, mean SBP and DBP was 132.6 and 85.7 mm Hg in amiloride and HCTZ-treated patients (P value not reported). At week nine, mean serum potassium levels were 4.13 and 3.98 mEq/L in triamterene and HCTZ- and amiloride and HCTZ-treated patients (P<0.05). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
All patients received placebo for 3 weeks prior to the treatment phase. After 2 weeks of treatment, dosage could be doubled.				
Hannson et al.[30] (1999) HYPERTENSION -2 (STOP) <u>Conventional drug group</u> Atenolol 50 mg QD, HCTZ 25 mg QD plus amiloride 2.5 mg QD, metoprolol 100 mg QD, or pindolol 5 mg QD vs <u>Newer drug group</u> ACE inhibitors (enalapril 10 mg QD or lisinopril 10 mg QD) or calcium channel blockers (felodipine 2.5 mg QD, or isradipine 2 to 5 mg QD)	BE, MC, OL, RCT Swedish men and women between 70 to 84 years old with treated or untreated essential with HTN on 3 separate occasions defined by SBP ≥180 mm Hg, DBP >105 mm Hg, or both	N=6,614 60 months	Primary: Combined fatal stroke, MI, and other fatal cardiovascular disease; combined fatal and nonfatal stroke, MI, and other cardiovascular Mortality Secondary: Not reported	Primary: The combined fatal mortality endpoints occurred in 221of the 2,213 patients in the conventional drugs group and in 438 of 4,401 in the newer drugs group (RR, 0.99; 95% CI, 0.84 to 1.16; P=0.89). The combined fatal and nonfatal mortality endpoints occurred in 460 patients taking conventional drugs and in 887 taking newer drugs (RR, 0.96; 95% CI, 0.86 to 1.08; P=0.49). Secondary: Not reported
Williams et al.[31]	3 phase, OL	N=156	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1984) Phase 1 (Baseline, 2 weeks): Triamterene and HCTZ 75-50 mg/day (fixed-dose combination product) (Group 1) vs triamterene and HCTZ 150-100 mg/day (fixed-dose combination product) (Group 3) vs no antihypertensive medications (Group 3) Phase 2 (4 weeks): Triamterene and HCTZ 75-50 mg/day (fixed-dose combination product) (Groups 1, 2 and 3) Phase 3 (up to 8 months): Triamterene and HCTZ 75-50	Patients 21 to 70 years of age, with essential HTN	6 to 32 weeks	Blood pressure and weight comparisons between Phase 1 and 2 Secondary: Serum potassium concentrations	During Phase 1, mean standing DBP, mean standing SBP and weight for Group 1-treated patients were: 91 mm Hg, 138 mm Hg and 82 kg (P values not reported). During Phase 2, the comparisons in these patients were: 88 mm Hg, 135 mm Hg and 82 kg (P values not reported). During Phase 1, mean standing DBP, mean standing SBP and weight for Group 2-treated patients were: 93 mm Hg, 139 mm Hg and 87 kg (P values not reported). During Phase 2, the comparisons in these patients were: 98 mm Hg, 149 mm Hg and 79 kg (P value not reported). During Phase 1, mean standing DBP, mean standing SBP and weight for Group 3-treated patients were: 98 mm Hg, 149 mm Hg and 80 kg (P values not reported). During Phase 2, the comparisons in these patients were: 94 mm Hg, 136 mm Hg and 78 kg (P value not reported). Of these Phase 1 and 2 comparisons, mean standing DBP and SBP differences were reported to be significant during Phase 2 for Group 1- and Group 3-treated patients (P values not reported). Secondary: When Group 2-treated patients were switched 75/50 mg/day, no patient became hypokalemic (serum potassium concentration <3.5 mEq/L) (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day (fixed-dose combination product) (Groups 1, 2 and 3)				
Hannson et al.[32] (2000) NORDIL Conventional therapy (diuretic, β-blocker or both) vs diltiazem 180 to 360 mg QD	BE, MC, OL, PRO, RCT Patients 50 to 74 years of age with DBP ≥100 mm Hg and previously untreated	N=10,881 4.5 years	Primary: Combined fatal and nonfatal stroke, fatal and nonfatal MI, other cardiovascular death Secondary: Fatal plus nonfatal stroke and fatal plus nonfatal MI	Primary: The primary endpoint occurred in 403 of the diltiazem patients and 400 of the diuretic/β-blocker patients (RR, 1.00; 95% CI, 0.87 to 1.15; P=0.97). Secondary: Rates of secondary endpoints were similar between the groups. Fatal plus nonfatal stroke occurred in 159 of the diltiazem patients and 196 of the diuretic/β-blocker patients (P=0.04). Fatal plus nonfatal MI occurred in 183 of the diltiazem patients and 157 of the diuretic/β-blocker patients (P=0.17). Other endpoints were not statistically different between the groups including cardiovascular death (P=0.41), all cardiac events (P=0.57 and congestive heart failure (P=0.42).
Messerli et al.[33] (1998) Diuretics (amiloride, chlorthalidone, HCTZ, HCTZ and triamterene [fixed-dose combination product], or thiazide) vs β-blockers (atenolol, metoprolol or pindolol)	MA 10 RCTs lasting ≥1 year, which used as first line agents diuretics and/or β-blockers and reported morbidity and mortality outcomes in patients ≥60 years of age with HTN	N=16,164 1 year	Primary: Cardiovascular morbidity and mortality, all-cause morbidity Secondary: Not reported	Primary: Diuretic treatment significantly reduced the odds for cardiovascular mortality by 25% (OR, 0.75; 95% CI, 0.64 to 0.87), while β-blockers did not reduce cardiovascular mortality (OR, 0.98; 95% CI, 0.78 to 1.23; P values not reported). Diuretic treatment significantly reduced the odds for all-cause mortality by 14% (OR, 0.86; 95% CI, 0.77 to 0.96), while β-blockers did not reduce all-cause mortality (OR, 1.05; 95% CI, 0.88 to 1.25; P values not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Lindholm et al.[34] (2005) β-blocker therapy (atenolol, metoprolol, oxprenolol*, pindolol or propranolol) vs other antihypertensive therapies (amiloride, amlodipine, bendro-flumethiazide, captopril, diltiazem, enalapril, felodipine, HCTZ, isradipine, lacidipine, lisinopril, losartan or verapamil) or placebo	MA 13 RCTs evaluating the treatment of primary HTN with a β-blocker as first line treatment (in ≥50% of all patients in one treatment group) and outcome data for all-cause mortality, cardiovascular morbidity or both	N=105,951 2.1 to 10.0 years	Primary: Stroke, MI, all-cause mortality Secondary: Not reported	Primary: The RR of stroke was 16% higher with β-blocker therapy than for the comparator therapies (RR, 1.16; 95% CI, 1.04 to 1.30; P=0.009). The RR of stroke was the highest with atenolol (26% higher) compared to other non β-blockers (RR, 1.26%; 95% CI, 15 to 38; P<0.0001). The relative risk of MI was 2% higher for β- blocker therapy than for the comparator therapies (RR, 1.02; 95% CI, 0.93 to 1.12), which was not significant (P value not reported). The RR of all-cause mortality was 3% higher for β-blocker therapy than for the comparator therapies (RR, 1.16; 95% CI, 0.99 to 1.08; P=0.14). Secondary: Not reported
Wiysonge et al.[35] (2007) Other antihypertensive therapies (i.e.,	MA 13 RCTs evaluating patients ≥18 years of age with HTN	N=91,561 Duration varied	Primary: All-cause mortality Secondary: Stroke, CHD, cardiovascular	Primary: There was not a significant difference observed in all-cause mortality between β-blocker therapy and placebo (RR, 0.99; 95% CI, 0.88 to 1.11; P value not reported), diuretics (RR, 1.04; 95% CI, 0.91 to 1.19; P value not reported) or renin-angiotensin system inhibitors (RR, 1.10; 95% CI, 0.98 to 1.24; P value not reported). There was a significantly higher rate in all-cause mortality with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo, diuretics, calcium channel blockers, or renin-angiotensin system inhibitors) vs β-blockers (atenolol, metoprolol, oxprenolol*, or propranolol)			death, total cardiovascular disease, adverse reactions	β-blocker therapy compared to calcium channel blockers (RR, 1.07; 95% CI, 1.00 to 1.14; P=0.04). Secondary: There was a significant decrease in stroke observed with β-blocker therapy compared to placebo (RR, 0.80; 95% CI, 0.66 to 0.96). Also there was a significant increase in stroke with β-blocker therapy compared to calcium channel blockers (RR, 1.24; 95% CI, 1.11 to 1.40) and renin-angiotensin system inhibitors (RR, 1.30; 95% CI, 1.11 to 1.53), but there was no difference observed compared to diuretics (RR, 1.17; 95% CI, 0.65 to 2.09). CHD risk was not significantly different between β-blocker therapy and placebo (RR, 0.93; 95% CI, 0.81 to 1.07]), diuretics (RR, 1.12; 95% CI, 0.82 to 1.54), calcium channel blockers (RR, 1.05; 95% CI, 0.96 to 1.15) or renin-angiotensin system inhibitors (RR, 0.90; 95% CI, 0.76 to 1.06). The risk of total cardiovascular disease was lower with β-blocker therapy compared to placebo (RR, 0.88; 95% CI, 0.79 to 0.97). The effect of β-blocker therapy on cardiovascular disease was significantly worse than that of calcium channel blockers (RR, 1.18; 95% CI, 1.08 to 1.29), but was not significantly different from that of diuretics (RR, 1.13; 95% CI, 0.99 to 1.28) or renin-angiotensin system inhibitors (RR, 1.00; 95% CI, 0.72 to 1.3). There was a significantly higher rate of discontinuation due to side effects with β-blocker therapy compared to diuretics (RR, 1.86; 95% CI, 1.39 to 2.50) and renin-angiotensin system inhibitors (RR, 1.41; 95% CI, 1.29 to 1.54), but there was no significant difference compared to calcium channel blockers (RR, 1.20; 95% CI, 0.71 to 2.04). Actual side effects were not reported.

*Agent not available in the United States.
Drug regimen abbreviations: BID=twice daily, QD=once daily
Study regimen abbreviations: BE=blinded endpoint, DB=double blind, MA=meta analysis, MC=multicenter, OL=open label, OS=observational, PC=placebo controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, SB=single blind, SR=systematic review, XO=cross over
Miscellaneous abbreviations: ACE inhibitor=angiotensin converting enzyme inhibitor, ARB=angiotensin II receptor blocker, CHD=coronary heart disease, CHF=congestive heart failure, CI=confidence interval, DBP=diastolic blood pressure, HCTZ=hydrochlorothiazide, HTN=hypertension, MI=myocardial infarction, NNT=number needed to treat, NYHA=New York Heart Association, OR=odds ratio, RR=relative risk, SBP=systolic blood pressure, WMD=weighted mean difference

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 11. Relative Cost of the Potassium-Sparing Diuretics

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Amiloride	tablet	N/A	N/A	$$
Triamterene	capsule	N/A	N/A	$$$$
Combination Products				
Amiloride and HCTZ	tablet	N/A	N/A	$
Triamterene and HCTZ	capsule, tablet	N/A	N/A	$

*Generic is available in at least one dosage form or strength.
HCTZ=hydrochlorothiazide, N/A=Not available

X. Conclusions

The potassium-sparing diuretics are approved for the treatment of congestive heart failure, edema, and hypertension.[1-3] When used alone, potassium-sparing diuretics have a weak diuretic and antihypertensive effect and an increased risk of hyperkalemia. The potassium-sparing diuretics are generally used in combination with other diuretics to help restore normal serum potassium levels or to prevent the development of hypokalemia.[1-3] Amiloride and triamterene are available as a fixed-dose combinations with hydrochlorothiazide. All of the products are available in a generic formulation.

For the treatment of chronic heart failure, guidelines recommend the use of diuretics in all patients who have evidence of volume overload. The loop diuretics are generally recommended as initial therapy in patients with left ventricular dysfunction. For those with persistent fluid retention despite treatment with a loop diuretic, a thiazide diuretic or metolazone may be added to the regimen. In patients with normal left ventricular function, either a thiazide diuretic or loop diuretic may be used as initial therapy to manage fluid overload.[4-5] As indicated by the FDA-approved indications of the potassium-sparing diuretics, these agents are typically used as adjunctive therapy in patients receiving thiazide diuretics to prevent the development of hypokalemia or to restore normal serum potassium levels.[1-3] Triamterene may be used along or with other diuretics, either for its added diuretic effect or its potassium-sparing potential.[1-2]

There are several national and international organizations that have published guidelines on the treatment of hypertension.[7-15] Thiazide-type diuretics are frequently recommended as initial therapy in patients with uncomplicated hypertension. According to the National Heart, Lung, and Blood Institute's Eighth Report of The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8), thiazide-type diuretics should be utilized first-line for most patients with hypertension, either alone or in combination with another antihypertensive from a different medication class (e.g., ACE inhibitors, ARBs, β-blockers, calcium channel blockers).[7] Several guidelines consistently recommend that the selection of an antihypertensive agent be based on compelling indications for use.[9-15] Most patients will require more than one antihypertensive medication to achieve blood pressure goals.[9-15] The use of a fixed-dose combination product may simplify the treatment regimen and improve adherence.[9,10,13] However, there are no prospective, randomized trials that have demonstrated better clinical outcomes with a fixed-dose combination product compared to the coadministration of the individual components as separate formulations.

Amiloride has been shown to be effective for the treatment of edema and hypertension, as well as for the prevention of serum potassium loss in patients taking a thiazide or loop diuretic. Clinical trials have also demonstrated comparable efficacy with the fixed-dose combination of amiloride-hydrochlorothiazide and triamterene-hydrochlorothiazide in patients with hypertension and heart failure.[16-35]

There is insufficient evidence to support that one brand potassium-sparing diuretic is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand potassium-sparing diuretics within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand potassium-sparing diuretic is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Thiazide Diuretics
AHFS Class 402820
May 8, 2024

I. Overview

The thiazide diuretics are approved for the treatment hypertension and edema due to renal dysfunction. They are also approved as adjunctive therapy for the management of edema associated with congestive heart failure, hepatic cirrhosis, as well as corticosteroid and estrogen therapy.[1-3] The thiazide diuretics inhibit the reabsorption of sodium and chloride in the cortical thick ascending limb of the loop of Henle and the early distal tubules. This action leads to an increase in the urinary excretion of sodium and chloride in approximately equivalent amounts.[1-4] Additionally, increased potassium and bicarbonate excretion, decreased calcium excretion, and uric acid retention may be observed. During initial thiazide therapy a reduction in cardiac output and extracellular volume occurs. However, with chronic therapy cardiac output normalizes and both peripheral vascular resistance and extracellular volume are reduced. In general, similar therapeutic and adverse effects are seen when equipotent doses are used. Thiazide diuretics are generally recommended when the glomerular filtration rate is above 30 mL/min.[3-5]

The thiazide diuretics that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All of the agents are available in a generic formulation. This class was last reviewed in May 2022.

Table 1. Thiazide Diuretics Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Chlorothiazide	injection*, suspension	Diuril®	chlorothiazide
Hydrochlorothiazide	capsule, tablet	N/A	hydrochlorothiazide

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List
N/A=Not available

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the thiazide diuretics are summarized in Table 2.

Table 2. Treatment Guidelines Using the Thiazide Diuretics

Clinical Guideline	Recommendation(s)
American Heart Association/American College of Cardiology/ Heart Failure Society of America: **2022 AHA/ACC /HFSA Guideline for the Management of Heart Failure (2022)[6]**	<u>Treatment of Stage A heart failure (HF)</u> • Hypertension should be controlled in accordance with guideline-directed medication therapy for hypertension to prevent symptomatic HF. (LoE: A) • In patients with type 2 diabetes and either established CVD or at high cardiovascular risk, SGLT-2 inhibitors should be used to prevent hospitalizations for HF. (LoE: A) • In the general population, healthy lifestyle habits such as regular physical activity, maintaining normal weight, healthy dietary patterns, and avoiding smoking are helpful to reduce future risk of HF. (LoE: B) • Patients at risk of developing HF, natriuretic peptide biomarker-based screening followed by team-based care, including a cardiovascular specialist optimizing therapy, can be useful to prevent the development of LV dysfunction (systolic or diastolic) or new-onset HF. (LoE: B) <u>Treatment of Stage B heart failure</u> • In patients with LVEF≤40%, ACE inhibitors should be used to prevent HF and reduce mortality. (LoE: A) • In patients with a recent or remote history of MI or ACS, statins should be used to

Clinical Guideline	Recommendation(s)
	prevent symptomatic HF and adverse cardiovascular events. (LoE: A) • In patients with a recent MI and LVEF≤40% who are intolerant to ACE inhibitors, ARB should be used to prevent symptomatic HF and reduce mortality. (LoE: B) • In patients with a recent or remote history of MI or ACS and LVEF≤40%, evidence-based beta blockers should be used to reduce mortality. (LoE: B) • In patients who are at least 40 days post-MI with LVEF ≤30% and NYHA class I symptoms while receiving guideline-directed medication therapy and have reasonable expectation of meaningful survival for greater than one year, an implantable cardioverter-defibrillator is recommended for primary prevention of sudden cardiac death to reduce total mortality. (LoE: B) • In patients with LVEF ≤40%, beta blockers should be used to prevent symptomatic HF. (LoE: C) • In patients with LVEF ≤50%, thiazolidinediones should not be used because they increase the risk of HF, including hospitalizations. (LoE: B) • In patients with LVEF ≤50%, nondihydropyridine calcium channel blockers with negative inotropic effects may be harmful. (LoE: C) <u>Treatment for Stage C Heart Failure with Reduced Ejection Fraction (HFrEF)</u> • For patients with stage C HF, avoiding excessive sodium intake is reasonable to reduce congestive symptoms. (LoE: C) • In patients with HF who have fluid retention, diuretics are recommended to relieve congestion, improve symptoms, and prevent worsening HF. (LoE: B) • For patients with HF and congestive symptoms, addition of a thiazide (e.g., metolazone) to treatment with a loop diuretic should be reserved for patients who do not respond to moderate or high dose loop diuretics to minimize electrolyte abnormalities. (LoE: B) • In patients with HFrEF and NYHA class II to III symptoms, the use of an ARNI is recommended to reduce morbidity and mortality. (LoE: A) • In patients with previous or current symptoms of chronic HFrEF, the use of an ACE inhibitor is beneficial to reduce morbidity and mortality when the use of an ARNI is not feasible. (LoE: A) • In patients with previous or current symptoms of chronic HFrEF, who are intolerant to an ACE inhibitor because of cough or angioedema, and when the use of an ARNI is not feasible, the use of an ARB is recommended to reduce morbidity and mortality. (LoE: A) • In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality. (LoE: B) • ARNIs should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor. (LoE: B) • ARNI or ACE inhibitors should not be administered in patients with a history of angioedema. (LoE: C) • In patients with HFrEF, with current or previous symptoms, use of one of the three β-blockers proven to reduce mortality (e.g., bisoprolol, carvedilol, sustained-release metoprolol succinate) is recommended to reduce mortality and hospitalizations. (LoE: A) • In patients with HFrEF and NYHA class II to IV symptoms, a mineralocorticoid receptor antagonist (spironolactone or eplerenone) is recommended to reduce morbidity and mortality, if eGFR is >30 mL/min/1.73 m^2 and serum potassium is <5.0 mEq/L. Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely followed thereafter to minimize risk of hyperkalemia and renal insufficiency. (LoE: A) • In patients taking a mineralocorticoid receptor antagonist whose serum potassium cannot be maintained at <5.5 mEq/L, mineralocorticoid receptor antagonist should be discontinued to avoid life threatening hyperkalemia. (LoE: B)

Clinical Guideline	Recommendation(s)
	• In patients with symptomatic chronic HFrEF, SGLT-2 an inhibitor is recommended to reduce hospitalization for HF and cardiovascular mortality, irrespective of the presence of type 2 diabetes. (LoE: A) • The combination of hydralazine and isosorbide dinitrate is recommended to improve symptoms and reduce morbidity and mortality for patients self-identified as African Americans with NYHA class III to IV HFrEF receiving optimal therapy. (LoE: A) • In patients with current or previous symptomatic HFrEF who cannot be given first-line agents, such as an ARNI, ACE inhibitor or ARB because of drug intolerance or renal insufficiency, a combination of hydralazine and isosorbide dinitrate might be considered to reduce morbidity and mortality. (LoE: C) • In patients with HF class II to IV symptoms, omega-3 polyunsaturated fatty acid supplementation may be reasonable to use as adjunctive therapy to reduce mortality and cardiovascular hospitalizations. (LoE: B) • In patients with chronic HFrEF without specific indication (e.g., venous thromboembolism, atrial fibrillation, a previous thromboembolic event, or a cardioembolic source, anticoagulation is not recommended. (LoE: B) • Dihydropyridine and non-dihydropyridine calcium channel blockers are not recommended for patients with HFrEF. (LoE: A) • In patients with HFrEF, vitamins, nutritional supplements, and hormonal therapy are not recommended other than to correct specific deficiencies. (LoE: B) • In patients with HFrEF, class IC antiarrhythmic medication and dronedarone may increase risk of mortality. (LoE: A) • In patients with HFrEF, thiazolidinediones increase the risk of worsening HF symptoms and hospitalizations. (LoE: A) • In patients with type 2 diabetes and high cardiovascular risk, the DPP-4 inhibitors, saxagliptin and alogliptin, increase the risk of HF hospitalization and should be avoided in patients with HF. (LoE: B) • In patients with HFrEF, nonsteroidal anti-inflammatory drugs worsen HF symptoms and should be avoided or withdrawn whenever possible. (LoE: B) • For patients with symptomatic (NYHA class II to III) stable chronic HFrEF (LVEF ≤35%) who are receiving guideline-directed medical therapy, including a maximally tolerated dose of a beta blocker, and who are in sinus rhythm with a heart rate of ≥70 beats per minute at rest, ivabradine can be beneficial to reduce HF hospitalizations and cardiovascular death. (LoE: B) • In patients with symptomatic HFrEF despite guideline-directed medical therapy or who are unable to tolerate guideline-directed medical therapy, digoxin might be considered to decrease hospitalizations for HF. (LoE: B) • In select high-risk patients with HFrEF and recent worsening of HF already on guideline-directed medical therapy, an oral soluble guanylate cyclase stimulator (vericiguat) may be considered to reduce HF hospitalization and cardiovascular death. (LoE: B) <u>Pharmacological treatment for Stage C HF with mildly reduced EF and improved EF</u> • In patients with HF with mildly reduced EF, SGLT-2 inhibitors can be beneficial in decreasing HF hospitalizations and cardiovascular mortality. (LoE: B) • Among patients with current or previous symptomatic HF with mildly reduced EF (LVEF, 41 to 49%), use of evidence-based beta blockers for HFrEF, ARNI, ACE inhibitor or ARB, and mineralocorticoid receptor antagonists may be considered to reduce the risk of HF hospitalization and cardiovascular mortality, particularly among patients with LVEF on the lower end of this spectrum. (LoE: B) • In patients with HF with improved EF after treatment, guideline-directed medical therapy should be continued to prevent relapse of HF and LV dysfunction, even in patients who may become asymptomatic. (LoE: B)

Clinical Guideline	Recommendation(s)
	Pharmacological treatment for Stage C HF with preserved EF (HFpEF) • Patients with hypertension and HFpEF should have medication titrated to attain blood pressure targets in accordance with published clinical practice guidelines to prevent morbidity. (LoE: C) • SGLT-2 inhibitors can be beneficial in decreasing HF hospitalizations and cardiovascular mortality. (LoE: B) • In patients with HFpEF, the use of a mineralocorticoid receptor antagonist, ARB, or ARNI may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum. (LoE: B) • Routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or quality of life in patients with HFpEF is ineffective. (LoE: B) Treatment of Stage D (advanced/refractory) HF • For patients with advanced HF and hyponatremia, the benefit of fluid restriction to reduce congestive symptoms is uncertain. (LoE: C) • Continuous intravenous inotropic support is reasonable as "bridge therapy" in patients with HF (Stage D) refractory to guideline-directed medical therapy and device therapy who are eligible for and awaiting mechanical circulatory support or cardiac transplantation. (LoE: B) • In select patients with HF Stage D, despite optimal guideline-directed medical therapy and device therapy who are ineligible for either mechanical circulatory support or cardiac transplantation, continuous intravenous inotropic support may be considered as palliative therapy for symptom control and improvement in functional status. (LoE: B) • Long-term use of either continuous or intermittent, intravenous inotropic agents, for reasons other than palliative care or as a bridge to advanced therapies, is potentially harmful. (LoE: B)
European Society of Cardiology: **Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (2021)**[7]	Pharmacological treatments indicated in patients with (NYHA Class II-IV) heart failure with reduced ejection fraction • An ACE inhibitor is recommended, in addition to a β-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death. • A mineralocorticoid receptor antagonist (MRA) is recommended for patients with HFrEF, who remain symptomatic despite treatment with an ACE inhibitor and a β-blocker, to reduce the risk of HF hospitalization and death. • Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death. Dapagliflozin or empagliflozin are recommended, in addition to optimal medical therapy with an ACE-I/ARNI, a β-blocker and an MRA, for patients with HFrEF regardless of diabetes status. • Sacubitril-valsartan is recommended as a replacement for an ACE inhibitor to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE inhibitor, a β-blocker, and a mineralocorticoid receptor antagonist. • Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion. • Ivabradine should be considered to reduce the risk of HF hospitalization or cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm despite treatment with an evidence-based dose of β-blocker (or maximum tolerated dose below that), ACE inhibitor (or ARB), and a mineralocorticoid receptor antagonist (or ARB). • Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm who are unable to tolerate or have contraindications for a β-blocker. Patients should also receive an ACE inhibitor (or ARB) and a mineralocorticoid receptor antagonist (or ARB). • An ARB is recommended to reduce the risk of HF hospitalization and

Clinical Guideline	Recommendation(s)
	cardiovascular death in symptomatic patients unable to tolerate an ACE inhibitor (patients should also receive a β-blocker and mineralocorticoid receptor antagonist). • An ARB may be considered to reduce the risk of HF hospitalization and death in patients who are symptomatic despite treatment with a β-blocker who are unable to tolerate a mineralocorticoid receptor antagonist. • Vericiguat may be considered in patients in NYHA class II-IV who have had worsening HF despite treatment with an ACE-I (or ARNI), a β-blocker and an MRA to reduce the risk of CV mortality or HF hospitalization. • Hydralazine and isosorbide dinitrate should be considered in self-identified black patients with LVEF ≤35% or with an LVEF <45% combined with a dilated LV in NYHA Class III–IV despite treatment with an ACE-I a β-blocker and a mineralocorticoid receptor antagonist to reduce the risk of HF hospitalization and death. • Hydralazine and isosorbide dinitrate may be considered in symptomatic patients with HFrEF who can tolerate neither an ACE inhibitor nor an ARB (or they are contraindicated) to reduce the risk of death. • Digoxin is a treatment with less-certain benefits and may be considered in symptomatic patients in sinus rhythm despite treatment with an ACE inhibitor (or ARB), a β-blocker and a mineralocorticoid receptor antagonist, to reduce the risk of hospitalization (both all-cause and HF-hospitalizations). <u>Recommendations for treatment of patients with (NYHA class II-IV) heart failure with mildly reduced ejection fraction (HFmrEF)</u> • Diuretics are recommended in patients with congestion and HFmrEF in order to alleviate symptoms and signs. • An ACE inhibitor may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • An ARB may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • A β-blocker may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • An MRA may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • Sacubitril/valsartan may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. <u>Recommendations for treatment of patients with heart failure with preserved ejection fraction (HFpEF)</u> • It is recommended to screen patients with HFpEF for both cardiovascular and noncardiovascular comorbidities, which, if present, should be treated provided safe and effective interventions exist to improve symptoms, well-being and/or prognosis. • Diuretics are recommended in congested patients with HFpEF in order to alleviate symptoms and signs. <u>Recommendations for the primary prevention of heart failure in patients with risk factors for its development</u> • Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life. • Treatment with statins is recommended in patients at high risk of CV disease or with CV disease in order to prevent or delay the onset of HF, and to prevent HF hospitalizations. • SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with diabetes at high risk of CV

Clinical Guideline	Recommendation(s)
	disease or with CV disease in order to prevent HF hospitalizations. • Counselling against sedentary habit, obesity, cigarette smoking, and alcohol abuse is recommended to prevent or delay the onset of HF. <u>Recommendations for the initial management of patients with acute heart failure – pharmacotherapy</u> • Intravenous loop diuretics are recommended for all patients with acute HF admitted with signs/symptoms of fluid overload to improve symptoms. It is recommended to regularly monitor symptoms, urine output, renal function and electrolytes during use of intravenous diuretics. • Combination of a loop diuretic with thiazide type diuretic should be considered in patients with resistant oedema who do not respond to an increase in loop diuretic doses. • In patients with acute HF and SBP >110 mmHg, intravenous vasodilators may be considered as initial therapy to improve symptoms and reduce congestion. • Inotropic agents may be considered in patients with SBP <90 mmHg and evidence of hypoperfusion who do not respond to standard treatment, including fluid challenge, to improve peripheral perfusion and maintain end-organ function. • Inotropic agents are not recommended routinely, due to safety concerns, unless the patient has symptomatic hypotension and evidence of hypoperfusion. • A vasopressor, preferably norepinephrine, may be considered in patients with cardiogenic shock to increase blood pressure and vital organ perfusion. • Thromboembolism prophylaxis (e.g. with LMWH) is recommended in patients not already anticoagulated and with no contraindication to anticoagulation, to reduce the risk of deep venous thrombosis and pulmonary embolism. • Routine use of opiates is not recommended, unless in selected patients with severe/intractable pain or anxiety.
Eighth Joint National Committee (JNC 8): **2014 Evidence-based Guideline for the Management of High Blood Pressure in Adults (2014)[8]**	• Pharmacologic treatment should be initiated in patients ≥60 years of age to lower blood pressure at systolic blood pressure ≥150 mm Hg or diastolic blood pressure ≥90 mm Hg and to a goal systolic blood pressure <150 mm Hg and goal diastolic blood pressure <90 mm Hg. Adjustment of treatment is not necessary if treatment results in lower blood pressure and treatment is well tolerated and without adverse effects on health or quality of life. • In patients <60 years of age, pharmacologic treatment should be initiated to lower blood pressure at diastolic blood pressure ≥90 mm Hg to a goal diastolic blood pressure <90 mm Hg. • In patients <60 years of age, pharmacologic treatment should be initiated to lower blood pressure at systolic blood pressure ≥150 mm Hg to a goal diastolic blood pressure <140 mm Hg. • For patients ≥18 years of age with chronic kidney disease or diabetes, pharmacologic treatment should be initiated to lower blood pressure at systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg and to a goal systolic blood pressure <140 mm Hg and goal diastolic blood pressure <90 mm Hg. • Initial antihypertensive treatment for the general nonblack population, including those with diabetes, should include thiazide-type diuretic, calcium channel blocker (CCB), ACE inhibitor, or ARB. • Initial antihypertensive treatment for the general black population, including those with diabetes, should include thiazide-type diuretic or CCB. • For patients ≥18 years of age with chronic kidney disease regardless of race or diabetes status, initial (or add-on) treatment should include an ACE inhibitor or ARB to improve kidney outcomes. • The main goal of antihypertensive treatment is to attain and maintain goal blood pressure. • If goal blood pressure is not attained within a month of treatment, the dose of the

Clinical Guideline	Recommendation(s)
	initial drug should be increased or second drug from the thiazide-type diuretic, CCB, ACE inhibitor, or ARB classes should be added. • If goal is not achieved with two drugs, a third drug from the thiazide-type diuretic, CCB, ACE inhibitor, or ARB classes should be added. • An ACE inhibitor and ARB should not be used together. • Antihypertensive classes can be used if the patient is unable to achieve goal blood pressure with three agents or had a contraindication to a preferred class. • If blood pressure is not able to be achieved or in complicated patients, referral to a hypertension specialist may be indicated.
International Society of Hypertension: **Global Hypertension Practice Guidelines (2020)[9]**	<u>Lifestyle modifications</u> • Lifestyle modification is the first line of antihypertensive treatment. • Salt reduction: Reduce salt added when preparing foods, and at the table. Avoid or limit consumption of high salt foods such as soy sauce, fast foods and processed food including breads and cereals high in salt. • Healthy diet: Eating a diet that is rich in whole grains, fruits, vegetables, polyunsaturated fats and dairy products and reducing food high in sugar, saturated fat and trans fats, such as the DASH diet. • Healthy drinks: Moderate consumption of coffee, green and black tea. Other beverages that can be beneficial include karkadé (hibiscus) tea, pomegranate juice, beetroot juice and cocoa. • Moderation of alcohol consumption: The recommended daily limit for alcohol consumptions is 2 standard drinks for men and 1.5 for women (10 g alcohol/standard drink). Avoid binge drinking. • Weight reduction: Body weight control is indicated to avoid obesity. Particularly abdominal obesity should be managed. Ethnic-specific cut-offs for BMI and waist circumference should be used. Alternatively, a waist-to-height ratio <0.5 is recommended for all populations. • Smoking cessation: Smoking is a major risk factor for cardiovascular disease (CVD), COPD and cancer. Smoking cessation and referral to smoking cessation programs are advised. • Regular physical activity: Studies suggest that regular aerobic and resistance exercise may be beneficial for both the prevention and treatment of hypertension. Moderate intensity aerobic exercise (walking, jogging, cycling, yoga, or swimming) for 30 minutes on five to seven days per week Strength training also can help reduce blood pressure. Performance of resistance/strength exercises on two to three days per week. • Reduce stress and induce mindfulness: Stress should be reduced and mindfulness or meditation introduced into the daily routine. • Reduce exposure to air pollution and cold temperature: Evidence from studies support a negative effect of air pollution on blood pressure in the long-term. <u>Pharmacological Treatment</u> • Ideal characteristics of drug treatment o Treatments should be evidence-based in relation to morbidity/mortality prevention. o Use a once-daily regimen which provides 24-hour blood pressure control. o Treatment should be affordable and/or cost-effective relative to other agents. o Treatments should be well-tolerated. o Evidence of benefits of use of the medication in populations to which it is to be applied. • General scheme for drug treatment o Lifestyle modification is the first line of antihypertensive treatment. o Grade 1 hypertension (BP 140 to 159/ 90 to 99): Immediate drug treatment in high-risk patients or those with CVD, chronic kidney disease

Clinical Guideline	Recommendation(s)
	(CKD), diabetes mellitus (DM), or hypertension-mediated organ damage (HMOD). Drug treatment after three to six months of lifestyle intervention if BP still not controlled in low to moderate risk patients. o Grade 2 hypertension (BP ≥160/100): Immediate drug treatment in all patients. • Core drug-treatment strategy o Step 1: Dual low-dose combination (ACE inhibitor or ARB plus dihydropyridine-calcium channel blockers (DHP-CCB)); consider monotherapy in low-risk grade 1 hypertension or in very old (≥80 years) or frail patients; consider ACE/ARB plus thiazide-like diuretic in post-stroke, very elderly, incipient HF, or CCB intolerance; consider ACE/ARB plus DHP-CCB or DHP-CCB plus thiazide-like diuretics in black patients. o Step 2: Dual full-dose combination (ACE inhibitor or ARB plus DHP-CCB); consider monotherapy in low-risk grade 1 hypertension or in very old (≥80 years) or frail patients; consider ACE/ARB plus thiazide-like diuretic in post-stroke, very elderly, incipient HF, or CCB intolerance. o Step 3: Triple combination (ACE/ARB plus DHP-CCB plus thiazide-like diuretic). o Step 4, resistant hypertension: triple combination plus spironolactone or other drug, alternatives include amiloride, doxazosin, eplerenone, clonidine, or β-blocker. Caution with spironolactone or other potassium sparing diuretics when estimated GFR <45 mL/min/1.73m^2 or K+ >4.5 mmol/L. o Consider β-blockers at any treatment step when there is a specific indications for their use, e.g., heart failure, angina, post-MI, atrial fibrillation, or younger women planning pregnancy or pregnant.
Hypertension Canada: **2020 Guidelines for the Prevention, Diagnosis, Risk Assessment, and Treatment of Hypertension in Adults and Children (2020)[10]**	<u>Indications for drug therapy for adults with hypertension without compelling indications for specific agents</u> • Antihypertensive therapy should be prescribed for average diastolic blood pressure (DBP) measurements of ≥100 mmHg or average systolic blood pressure (SBP) measurements of ≥160 mmHg in patients without macrovascular target organ damage or other cardiovascular risk factors. • Antihypertensive therapy should be strongly considered for average DPB readings ≥90 mmHg or for average SBP readings ≥140 mmHg in the presence of macrovascular target organ damage or other independent cardiovascular risk factors. • For high-risk patients, aged 50 years or older, with SBP levels ≥130 mmHg, intensive management to target a SBP <120 mmHg should be considered. Patient selection for intensive management is recommended and caution should be taken in certain high-risk groups. <u>Indications for drug therapy for adults with diastolic and with or without systolic hypertension</u> • Initial therapy should be with either monotherapy or single pill combination (SPC). o Recommended monotherapy choices are: ▪ A thiazide/thiazide-like diuretic, with longer-acting diuretics preferred; ▪ A β-blocker (in patients <60 years of age); ▪ An angiotensin-converting enzyme (ACE) inhibitor (in nonblack patients); ▪ An angiotensin receptor blocker (ARB); or ▪ A long-acting calcium channel blocker (CCB). o Recommended SPC choices are those in which an ACE inhibitor is combined with a CCB, ARB with a CCB, or ACE inhibitor or ARB with a diuretic.

Clinical Guideline	Recommendation(s)
	○ Hypokalemia should be avoided in patients treated with thiazide/thiazide-like diuretic monotherapy. • Additional antihypertensive drugs should be used if target BP levels are not achieved with standard-dose monotherapy. Add-on drugs should be chosen from first-line choices. Useful choices include a thiazide/thiazide-like diuretic or CCB with either: ACE inhibitor, ARB, or β-blocker. Caution should be exercised in combining a nondihydropyridine CCB and a β-blocker. The combination of an ACE inhibitor and an ARB is not recommended. • If BP is still not controlled with a combination of two or more first-line agents, or there are adverse effects, other antihypertensive drugs may be added. • Possible reasons for poor response to therapy should be considered. • α-Blockers are not recommended as first-line agents for uncomplicated hypertension; β-blockers are not recommended as first-line therapy for uncomplicated hypertension in patients ≥60 years of age; and ACE inhibitors are not recommended as first-line therapy for uncomplicated hypertension in black patients. However, these agents may be used in patients with certain comorbid conditions or in combination therapy. <u>Indications for drug therapy for adults with isolated systolic hypertension</u> • Initial therapy should be single-agent therapy with a thiazide/thiazide-like diuretic, a long-acting dihydropyridine CCB, or an ARB. If there are adverse effects, another drug from this group should be substituted. Hypokalemia should be avoided in patients treated with thiazide/thiazide-like diuretic monotherapy. • Additional antihypertensive drugs should be used if target BP levels are not achieved with standard-dose monotherapy. Add-on drugs should be chosen from first-line options. • If BP is still not controlled with a combination of two or more first-line agents, or there are adverse effects, other classes of drugs (such as α-blockers, ACE inhibitors, centrally acting agents, or nondihydropyridine CCBs) may be combined or substituted. • Possible reasons for poor response to therapy should be considered. • α-Blockers are not recommended as first-line agents for uncomplicated isolated systolic hypertension; and β-blockers are not recommended as first-line therapy for isolated systolic hypertension in patients ≥60 years of age. However, both agents may be used in patients with certain comorbid conditions or in combination therapy. <u>Guidelines for hypertensive patients with coronary artery disease (CAD)</u> • For most hypertensive patients with CAD, an ACE inhibitor or ARB is recommended. • For hypertensive patients with CAD, but without coexisting systolic heart failure, the combination of an ACE inhibitor and ARB is not recommended. • For high-risk hypertensive patients, when combination therapy is being used, choices should be individualized. The combination of an ACE inhibitor and a dihydropyridine CCB is preferable to an ACE inhibitor and a thiazide/thiazide-like diuretic in selected patients. • For patients with stable angina pectoris but without previous heart failure, myocardial infarction, or coronary artery bypass surgery, either a β-blocker or CCB can be used as initial therapy. • Short-acting nifedipine should not be used. • When decreasing SBP to target levels in patients with established CAD (especially if isolated systolic hypertension is present), be cautious when the DBP is ≤60 mmHg because of concerns that myocardial ischemia might be exacerbated, especially in patients with left ventricular hypertrophy (LVH).

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	Guidelines for patients with hypertension who have had a recent myocardial infarction
	• Initial therapy should include a β-blocker as well as an ACE inhibitor.
	• An ARB can be used if the patient is intolerant of an ACE inhibitor.
	• CCBs may be used in patients after myocardial infarction when β-blockers are contraindicated or not effective. Nondihydropyridine CCBs should not be used when there is heart failure, evidenced by pulmonary congestion on examination or radiography.
	
	Treatment of hypertension in association with heart failure
	• In patients with systolic dysfunction (ejection fraction <40%), ACE inhibitors and β-blockers are recommended for initial therapy. Aldosterone antagonists (mineralocorticoid receptor antagonists) may be combined in treatment for patients with a recent cardiovascular hospitalization, acute myocardial infarction, elevated B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide level, or New York Heart Association (NYHA) Class II-IV symptoms. Careful monitoring for hyperkalemia is recommended when combining an aldosterone antagonist with ACE inhibitor or ARB treatment. Other diuretics are recommended as additional therapy if needed. Beyond considerations of BP control, doses of ACE inhibitors or ARBs should be titrated to those reported to be effective in trials unless adverse effects become manifest.
	• An ARB is recommended if ACE inhibitors are not tolerated.
	• A combination of hydralazine and isosorbide dinitrate is recommended if ACE inhibitors and ARBs are contraindicated or not tolerated.
	• For hypertensive patients whose BP is not controlled, an ARB may be combined with an ACE inhibitor and other antihypertensive drug treatment. Careful monitoring should be used if combining an ACE inhibitor and an ARB because of potential adverse effects such as hypotension, hyperkalemia, and worsening renal function. Additional therapies may also include dihydropyridine CCBs.
	• An angiotensin receptor-neprilysin inhibitor (ARNI) should be used in place of an ACE inhibitor or ARB for patients with HFrEF (<40%) who remain symptomatic despite treatment with appropriate dose of guideline directed HF therapy. Eligible patients must have a serum potassium <5.2 mmol/L, an eGFR ≤30 mL/min/1.73m^2 and close surveillance of serum potassium and creatinine.
	
	Treatment of hypertension in association with stroke
	• BP management in acute ischemic stroke (onset to 72 hours)
	  ○ Please refer to Stroke Best Practice recommendations.
	• BP management after acute ischemic stroke
	  ○ Strong consideration should be given to the initiation of antihypertensive therapy after the acute phase of a stroke or transient ischemic attack.
	  ○ After the acute phase of a stroke, BP-lowering treatment is recommended to a target of consistently <140/90 mmHg.
	  ○ Treatment with an ACE inhibitor and thiazide/thiazide-like diuretic combination is preferred.
	  ○ For patients with stroke, the combination of an ACE inhibitor and ARB is not recommended.
	• BP management in hemorrhagic stroke (onset to 72 hours)
	  ○ Please refer to Stroke Best Practice recommendations.
	
	Treatment of hypertension in association with LVH
	• Hypertensive patients with LVH should be treated with antihypertensive therapy to decrease the rate of subsequent cardiovascular events.
	• The choice of initial therapy can be influenced by the presence of LVH. Initial therapy can be drug treatment using ACE inhibitors, ARBs, long-acting CCBs, or thiazide/thiazide-like diuretics. Direct arterial vasodilators such as hydralazine or

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	minoxidil should not be used. Treatment of hypertension in association with nondiabetic chronic kidney disease • Individualize BP targets in patients with chronic kidney disease. Consider intensive targets (SBP <120 mmHg) in appropriate patients. • For patients with hypertension and proteinuric chronic kidney disease (urinary protein >150 mg per 24 hours or albumin to creatinine ratio >30 mg/mmol), initial therapy should be an ACE inhibitor or an ARB if there is intolerance to ACE inhibitors. • In most cases, combination therapy with other antihypertensive agents might be needed to reach target BP levels. • The combination of an ACE inhibitor and ARB is not recommended for patients with nonproteinuric chronic kidney disease. Treatment of hypertension in association with renovascular disease • Patients with hypertension attributable to atherosclerotic renal artery stenosis should be primarily medically managed because renal angioplasty and stenting offers no benefit over optimal medical therapy alone. • Renal artery angioplasty and stenting for atherosclerotic hemodynamically significant renal artery stenosis could be considered for patients with uncontrolled hypertension resistant to maximally tolerated pharmacotherapy, progressive renal function loss, and acute pulmonary edema. • Patients with confirmed renal fibromuscular dysplasia (FMD) should be referred to a hypertension specialist. • Renal artery angioplasty without stenting is recommended for treatment of FMD-related renal artery stenosis. Stenting is not recommended unless needed because of a periprocedural dissection. Surgical revascularization should be considered in cases of complex lesions less amendable to angioplasty, stenosis associated with complex aneurysm, and restenosis despite two unsuccessful attempts of angioplasty. Treatment of hypertension in association with diabetes mellitus • Persons with diabetes mellitus should be treated to attain SBP of <130 mmHg and DBP of <80 mmHg. • For persons with cardiovascular or kidney disease, including microalbuminuria, or with cardiovascular risk factors in addition to diabetes and hypertension, an ACE inhibitor or an ARB is recommended as initial therapy. • For persons with diabetes and hypertension not included in other guidelines in this section, appropriate choices include (in alphabetical order): ACE inhibitors, ARBs, dihydropyridine CCBs, and thiazide/thiazide-like diuretics. • If target BP levels are not achieved with standard-dose monotherapy, additional antihypertensive therapy should be used. For persons in whom combination therapy with an ACE inhibitor is being considered, a dihydropyridine CCB is preferable to a thiazide/thiazide-like diuretic. Resistant hypertension • Resistant hypertension is defined as BP above target despite three or more BP-lowering drugs at optimal doses preferably including a diuretic (and usually a renin-angiotensin-aldosterone system blocker and a CCB. • Accurate office and out-of-office BP measurement is essential. • Other reasons for apparent resistant hypertension should be eliminated before diagnosing true resistant hypertension, including nonadherence, white coat effect, and secondary hypertension. • Pharmacotherapy with the additional use of spironolactone, bisoprolol, doxazosin, amiloride, eplerenone, or clonidine with the baseline regimen decreases BP

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	significantly, with the greatest BP-lowering shown with spironolactone. • Patients with resistant hypertension should be referred to providers with expertise in diagnosis and management of hypertension. Hypertension and pediatrics • BP should be measured regularly in children three years of age or older; the auscultatory method is the gold-standard at present. • Initial therapy should be monotherapy, with an ACE inhibitor or ARB (not first-line in black children), or a long-acting dihydropyridine CCB. • The treatment t goal is systolic and diastolic office BP and/or ABPM < 95th percentile or <90th percentile in children with risk factors or target organ damage. • Complex cases should be referred to an expert in pediatric hypertension. Hypertension and pregnancy • Up to 7% of pregnancies are complicated by a hypertensive disorder of pregnancy, and approximately 5% of women will have chronic hypertension when they become pregnant. • The prevalence of hypertension in pregnancy is expected to increase with women becoming pregnant later in their reproductive years and the increasing prevalence of cardiovascular comorbidities such as increased preconception body mass index and maternal diabetes. • The possibility of pregnancy should be considered when managing women with hypertension who are of reproductive age. • Preconception counselling should be offered to all women with hypertension who are considering pregnancy. • ACE inhibitor and ARB therapy should be avoided before conception and during pregnancy unless there is a compelling indication for their use (i.e., proteinuric kidney disease). • Hypertension during pregnancy can increase the risk of adverse maternal and fetal outcomes, including an increased risk of preeclampsia, placental abruption, prematurity, small for gestational age infants, stillbirth, and maternal renal and retinal injury, thus generally requires involvement of an interdisciplinary team including obstetrical care providers. • Antihypertensive therapy is recommended for average SBP measurements of ≥140 mmHg or DBP measurements of ≥90 mmHg in pregnant women with chronic hypertension, gestational hypertension, or preeclampsia. Initial antihypertensive therapy should be monotherapy from the following first-line drugs: oral labetalol, oral methyldopa, long-acting oral nifedipine, or other oral b-blockers (acebutolol, metoprolol, pindolol, and propranolol). Other antihypertensive drugs can be considered as second-line drugs including: clonidine, hydralazine, and thiazide diuretics. • Women with severe hypertension with SBP ≥160 mmHg or DBP ≥110 mmHg in pregnancy or postpartum require urgent antihypertensive therapy because it is considered an obstetrical emergency. • Antihypertensive drugs used in breastfeeding women include: labetalol, methyldopa, long-acting nifedipine, enalapril, or captopril.
European Society of Hypertension: **2023 Guidelines for the management of arterial hypertension (2023)**[11]	General recommendations for antihypertensive drug treatment • BP lowering should be prioritized over the selection of specific antihypertensive drug classes because treatment benefit largely originates from BP reduction. • Five major drug classes including, ACE inhibitors, ARBs, β-blockers, CCBs, and Thiazide/Thiazide-like diuretics have effectively reduced blood pressure and cardiovascular events in randomized controlled trials. These drugs and their combinations are recommended as the basis of antihypertensive treatment strategies. • Initiation of therapy with a two-drug combination is recommended for most

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	hypertensive patients. Preferred combinations should comprise a RAS blocker (either an ACE inhibitor or an ARB) with a CCB or thiazide/thiazide-like diuretic. Other combinations of the five major drug classes can be used. • Initiation with monotherapy can be considered in patients with: grade 1 hypertension and low-risk if BP is only marginally elevated (less than 150 mmHg SBP and 95 mmHg DBP) high-normal BP and very high cardiovascular risk, frailty and/or and advance age. • If BP is not controlled with the initial two-drug combination by using the maximum recommended and tolerated dose of the respective components, treatment should be increased to a three-drug combination, usually a RAS blocker plus CCB plus thiazide/thiazide-like diuretic. • If BP is not controlled with a three-drug combination by using the maximum recommended and tolerated dose of the respective components, it is recommended to extend treatment according to the recommendations for resistant hypertension. • The use of single pill combinations should be preferred at any treatment step (i.e. during initiation of therapy with a two-drug combination and at any other step of treatment). • β-blocker should be used at initiation of therapy or at any treatment step as guideline-directed medical therapy (e.g., heart failure with reduced ejection fraction, anti-ischemic therapy in chronic coronary syndromes, heart rate control in atrial fibrillation). • β-blockers can be considered in the presence of several other conditions in which their use can be favorable. • The combination of two RAS blockers is not recommended due to increased risk of adverse events, in particular AKI. True-resistant hypertension • In resistant hypertension, it is recommended to reinforce lifestyle measures. • Drugs that can be considered as additional therapy in patients with resistant hypertension are preferably spironolactone (or other MRA), or β-blocker or Alpha-1 blockers or centrally acting agents (clonidine), or amiloride. • Thiazide/thiazide-like diuretics are recommended in resistant hypertension if estimated eGFR is ≥30 mL/min/1.73m^2. • Loop diuretics may be considered in patients with an estimated eGFR < 45 mL/min/1.73m^2 and should be used if eGFR falls below 30 mL/min/1.73m^2. • Chlorthalidone (12.5 to 25 mg once daily) could be used with or without a loop diuretic if eGFR is <30 mL/min/1.73m^2. • Renal deprivation can be considered as an additional treatment option in patients with resistant hypertension if eGFR is >40 mL/min/1.73m^2. • Patients with resistant hypertension should be followed very closely. Follow-up includes periodical ambulatory blood pressure monitoring and assessment of hypertension-mediated organ damage, particularly kidney function and serum potassium levels. Regular use of home blood pressure monitoring and monitoring of drug adherence are desirable.
National Institute for Health and Clinical Excellence: **Hypertension in adults: diagnosis and management (2019)**[12]	Choosing antihypertensive drug treatment (for people with or without type II diabetes) • Where possible, recommend treatment with drugs taken only once a day. • Prescribe non-proprietary drugs where these are appropriate and minimize cost. • Offer people with isolated systolic hypertension (systolic blood pressure ≥160 mmHg) the same treatment as people with both raised systolic and diastolic blood pressure. • Offer antihypertensive drug treatment to women of child-bearing potential with diagnosed hypertension in line with recommendations in this guideline. For women considering pregnancy or who are pregnant or breastfeeding, manage hypertension in line with the recommendations on Management of pregnancy with chronic hypertension and Breastfeeding in 'Hypertension in pregnancy'.

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	• When choosing antihypertensive drug treatment for adults of black African or African-Caribbean family origin, consider an angiotensin II receptor blocker, in preference to an angiotensin-converting enzyme inhibitor. Step one treatment • Patients <55 years of age should be offered a step one antihypertensive with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). • Offer an ACE inhibitor or an ARB to adults starting step 1 antihypertensive treatment who have type II diabetes and are of any age or family origin or those aged <55 years but not of black African or African-Caribbean family origin. • If an ACE inhibitor is not tolerated, offer an ARB. • Do not combine an ACE inhibitor with an ARB for the treatment of hypertension. • Offer a calcium channel blocker (CCB) to adults starting step 1 antihypertensive treatment who are >55 years of age and do not have diabetes and are of black African or African-Caribbean family origin and do not have type II diabetes and of any age. • If a CCB is not suitable, for example because of edema or intolerance, or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic. • If diuretic treatment is to be initiated or changed, offer a thiazide‑like diuretic, such as indapamide in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide. • For adults with hypertension who are already receiving treatment with bendroflumethiazide or hydrochlorothiazide, who have stable, well-controlled blood pressure, continue with their treatment. Step two treatment • Before considering next step treatment for hypertension discuss with the person if they are taking their medicine as prescribed and support adherence in line with NICE's guideline on "Medicines adherence: involving patients decisions about prescribed medicines and supporting adherence". • If hypertension is not controlled with a step one treatment of an ACE inhibitor or ARB, offer choice of one of the following drugs in addition to the step one treatment: a CCB or a thiazide-like diuretic. • If hypertension is not controlled in adults taking step one treatment of a CCB, offer the choice of one of the following drugs in addition to the step one treatment: an ACE inhibitor or an ARB or a thiazide-like diuretic. • If hypertension is not controlled in adults of black African or African–Caribbean family origin who do not have type 2 diabetes taking step one treatment, consider an ARB, in preference to an ACE inhibitor, in addition to step one treatment. Step three treatment • Before considering step three treatment, review the person's medications to ensure they are being taken at the optimal doses and discuss adherence (see recommendation under step two). • If hypertension is not controlled in adults taking step two treatment, offer a combination of an ACE inhibitor or ARB and a CCB and a thiazide-like diuretic. Step four treatment • If hypertension is not controlled in adults taking the optimal tolerated doses of an ACE inhibitor or an ARB plus a CCB and a thiazide-like diuretic, regard them as having resistant hypertension. • Before considering further treatment for a person with resistant hypertension, confirm elevated clinic blood pressure measurements using ambulatory or home

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	blood pressure recordings, assess for postural hypotension, and discuss adherence. • For people with confirmed resistant hypertension, consider adding a fourth antihypertensive drug as step four treatment or seeking specialist advice. • Consider further diuretic therapy with low-dose spironolactone for adults with resistant hypertension starting step four treatment who have a blood potassium level of 4.5 mmol/l or less. Use particular caution in people with a reduced estimated glomerular filtration rate because they have an increased risk of hyperkalemia. • When using further diuretic therapy for step four treatment of resistant hypertension, monitor blood sodium and potassium and renal function within one month of starting treatment and repeat as needed thereafter. • Consider an alpha-blocker or beta-blocker for adults with resistant hypertension starting step four treatment who have a blood potassium level of more than 4.5 mmol/l. • If blood pressure remains uncontrolled in people with resistant hypertension taking the optimal tolerated doses of four drugs, seek specialist advice.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in Blacks (2010)[13]**	• To attain and maintain blood pressure (BP) below target levels, multiple antihypertensive drugs will be required in most hypertensive blacks. • Use of two-drug combination therapy when SBP is >15 mm Hg and/or DBP is >10 mm Hg above goal levels is increasingly recommended as first-line therapy. • Two-drug regimens have generally contained a thiazide-type diuretic; however, the combination of a calcium channel blocker (CCB) with either an ACE inhibitor or an ARB has been shown equally efficacious in BP lowering but with demonstrated superiority (CCB+ACE) for hard clinical outcomes compared with the same ACE inhibitor plus a thiazide-type diuretic. • In secondary prevention patients, the combination therapy should include a drug(s) with the appropriate compelling indications. • Certain classes of antihypertensive medications, specifically diuretics and CCBs, lower BP on average more than β-blockers and renin-angiotensin system (RAS) blockers in black patients when used as monotherapies. • In the absence of compelling indications, when BP is near goal levels, monotherapy with a diuretic or a CCB is preferred. • Lifestyle modifications should be initiated in all patients with hypertension, whether or not pharmacotherapy is planned. • ACE inhibitors or ARBs are recommended as alternative monotherapy options in the treatment of hypertension in blacks. The rationale for their lower tier monotherapy recommendation is because they have consistently achieved lesser average reductions in BP relative to that observed with monotherapy using either a diuretic or CCB.
Kidney Disease Improving Clinical Outcomes Group: **KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease (2021)[14]**	<u>Blood pressure measurement</u> • The Work Group recommends standardized office blood pressure (BP) measurement in preference to routine office BP measurements for the management of high BP in adults. • The Work Group suggests that out-of-office BP measurements with ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM) be used to complement standardized office BP readings for the management of high BP. <u>Lifestyle interventions for lowering BP in patients with chronic kidney disease (CKD) not receiving dialysis</u> • The Work Group suggests targeting a sodium intake <2 grams of sodium per day (or <90 mmol of sodium per day, or <5 grams of sodium chloride per day) in patients with high BP and CKD. • The Work Group suggests that patients with high BP and CKD be advised to undertake moderate-intensity physical activity for a cumulative duration of at least 150 minutes per week, or to a level compatible with their cardiovascular and

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	physical tolerance. BP management in patients with CKD, with or without diabetes, not receiving dialysis • The Work Group suggests that adults with high BP and CKD be treated with a target systolic BP (SBP) of <120 mmHg, when tolerated, using standardized office BP measurement. • The Work Group recommends starting renin-angiotensin-system inhibitors (RASi) (angiotensin-converting enzyme inhibitor [ACEi] or angiotensin II receptor blocker [ARB]) for people with high BP, CKD, and severely increased albuminuria without diabetes. • The Work Group suggests starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately increased albuminuria without diabetes. • The Work Group recommends starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately-to-severely increased albuminuria with diabetes. • The Work Group recommends avoiding any combination of ACEi, ARB, and direct renin inhibitor (DRI) therapy in patients with CKD, with or without diabetes. BP management in kidney transplant recipients • Treat adults kidney transplant recipients with high BP to a target BP of <130 mmHg systolic and <80 mmHg diastolic using standardized office BP measurement. • The Work Group recommends that a dihydropyridine calcium channel blocker (CCB) or an ARB be used as the first-line antihypertensive agent in adult kidney transplant recipients. BP management in children with CKD • The Work Group suggests that in children with CKD, 24-hour mean arterial pressure by ABPM should be lowered to <50th percentile for age, sex, and height.
American College of Cardiology/ American Heart Association Task Force: **Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults (2017)**[15]	Initiation of Blood Pressure (BP) Treatment for Overall Cardiovascular Disease (CVD) Risk • Use of BP-lowering medications is recommended for secondary prevention of recurrent CVD events in patients with clinical CVD and an average systolic blood pressure (SBP) ≥130 mmHg or an average diastolic blood pressure (DBP) of ≥80 mmHg and for primary prevention in adults with an estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk of ≥10% and an average SBP of ≥130 mmHg or an average ≥80 mmHg. • Use of BP-lowering medication is recommended for primary prevention of CVD in adults with no history of CVD and with an estimated 10-year ASCVD risk <10% and an SBP of ≥140 mmHg or a DBP of ≥90 mmHg. • Simultaneous use of an angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), and/or renin inhibitor is potentially harmful and is not recommended to treat adults with hypertension. • For adults with confirmed hypertension and known CVD or 10-year ASCVD risk of ≥10%, a BP target <130/80 mmHg is recommended. For adults with confirmed hypertension without additional markers of increased CVD risk, a BP target <130/80 mmHg may be reasonable. • For initiation of antihypertensive drug therapy, first-line agents include thiazide diuretics, calcium channel blockers (CCBs), and ACE inhibitors or ARBs. • Initiation of antihypertensive drug therapy with two first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended in adults with stage 2 hypertension and an average BP >20/10 mmHg above their BP target. • Initiation of antihypertensive drug therapy with a single antihypertensive drug is reasonable in adults with stage 1 hypertension and BP goal <130/80 mmHg with

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	dosage titration and sequential addition of other agents to achieve the BP target. Stable Ischemic Heart Disease (SIHD) • In adults with SIHD and hypertension, a BP target <130/80 is recommended. • Adults with SIHD and hypertension (BP ≥130/80 mmHg) should be treated with medications [e.g., guideline-directed medical therapy (GDMT) beta-blockers, ACE inhibitors, or ARBs] for compelling indications [e.g., previous myocardial infarction (MI), stable angina] as first-line therapy, with the addition of other drugs (e.g., dihydropyridine CCBs, thiazide diuretics, and/or mineralocorticoid receptor antagonists) as needed to further control hypertension. • In adults with SIHD with angina and persistent uncontrolled hypertension, the addition of dihydropyridine CCBs to GDMT beta-blockers is recommended. • In adults who have had a MI or acute coronary syndrome, it is reasonable to continue GDMT beta-blockers beyond three years as long-term therapy for hypertension. • Beta-blockers and/or CCBs might be considered to control hypertension in patients with coronary artery disease (CAD) had an MI more than three years ago and have angina. Heart Failure • In adults with increased risk of HF, the optimal BP in those with hypertension should be <130 mmHg. • Adults with HFrEF and hypertension should be prescribed GDMT titrated to attain a BP <130/80 mmHg. • Non-dihydropyridine CCBs are not recommended in the treatment of hypertension in adults with HFrEF. • In adults with HFpEF who present with symptoms of volume overload, diuretics should be prescribed to control hypertension. • Adults with HFpEF and persistent hypertension after management of volume overload should be prescribed ACE inhibitors or ARBs and beta-blockers titrated to attain SBP <130 mmHg. CKD • Adults with hypertension and CKD should be treated to a BP goal <130/80 mmHg. • In adults with hypertension and CKD [stage 3 or higher or stage 1 or 2 with albuminuria (≥300 mg/d, or ≥300 mg/g albumin-to-creatinine ratio or the equivalent in the first morning void)], treatment with an ACE inhibitor is reasonable to slow kidney disease progression. Treatment with an ARB may be reasonable if an ACE inhibitor is not tolerated. • After kidney transplantation, it is reasonable to treat patients with hypertension to a BP goal <130/80 mmHg and with a CCB on the basis of improved glomerular filtration rate (GFR) and kidney survival. Cerebrovascular Disease • In adults with intracerebral hemorrhage (ICH) who present with SBP >220 mmHg, it is reasonable to use continuous intravenous (IV) drug infusion and close BP monitoring to lower levels. Immediate lowering of SBP to <140 mmHg in adults with spontaneous ICH who present within six hours of the acute event and have an SBP between 150 mmHg and 220 mmHg is not of benefit to reduce death or severe disability and can be potentially harmful. • Adults with acute ischemic stroke and elevated BP who are eligible for treatment with IV tissue plasminogen activator (tPA) should have their BP slowly lowered to <185/110 mmHg before thrombolytic therapy is initiated. • In adults with an acute ischemic stroke, BP should be <185/110 mmHg before administration of IV tPA and should be maintained below 180/105 mmHg for at

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	least the first 24 hours after initiation drug therapy. • Starting or restarting antihypertensive therapy during hospitalization in patients with BP >140/90 mmHg who are neurologically stable is safe and reasonable to improve long-term BP control, unless contraindicated. • In patient with BP ≥220/120 mmHg who did not receive IV alteplase or endovascular treatment and have no comorbid conditions requiring acute antihypertensive treatment, the benefit of initiating or reinitiating treatment of hypertension within the first 48 to 72 hours is uncertain. It might be reasonable to lower BP by 15% during the first 24 hours after onset of stroke. In patients with BP <220/120 mmHg with the same conditions, initiating or reinitiating treatment of hypertension within the first 48 to 72 hours after an acute ischemic stroke is not effective to prevent death or dependency. • Adults with previously treated stroke or transient ischemic attack should be restarted on antihypertensive treatment after the first few days of the index event to reduce the risk of recurrent stroke and other vascular events. Treatment with a thiazide diuretic, ACE inhibitor, or ARB, or combination treatment consisting of a thiazide diuretic plus ACE inhibitor, is useful. • Adults not previously treated for hypertension who experienced a stroke or transient ischemic attack and have an established BP ≥140/90 mmHg should be prescribed antihypertensive treatment a few days after the index event to reduce the risk of recurrent stroke and other vascular event. • For adults who experience a stroke or transient ischemic attack, selection of specific drugs should be individualized on the basis of patient comorbidities and agent pharmacological class. • For adults who experience a stroke or transient ischemic attack, a BP goal <130/80 mmHg may be reasonable. • For adults with a lacunar stroke, a target SBP goal <130 mmHg may be reasonable. • In adults previously untreated for hypertension who experience an ischemic stroke or transient ischemic attack and have an SBP <140 mmHg and a DBP <90 mmHg, the usefulness of initiating antihypertensive treatment is not well established. <u>Peripheral Artery Disease (PAD)</u> • Adults with hypertension and PAD should be treated similarly to patients with hypertension without PAD. <u>Diabetes Mellitus (DM)</u> • In adults with DM and hypertension, antihypertensive drug treatment should be initiated at a BP of ≥130/80 mmHg with a treatment goal <130/80 mmHg. • In adults with DM and hypertension, all first-line classes of antihypertensive agents (i.e., diuretics, ACE inhibitors, ARBs, and CCBs) are useful and effective. • In adults with DM and hypertension, ACE inhibitors or ARBs may be considered in the presence of albuminuria. <u>Atrial Fibrillation, Valvular Heart Disease, and Aortic disease</u> • Treatment of hypertension can be useful for prevention of recurrence of AF. • In adults with asymptomatic aortic stenosis, hypertension should be treated with pharmacotherapy, starting at a low dose and gradually titrating upward as needed. • In patients with chronic aortic insufficiency, treatment of systolic hypertension with agents that do not slow the heart rate (i.e., avoid beta-blockers) is reasonable. • Beta-blockers are recommended as the preferred antihypertensive agents in patients with hypertension and thoracic aortic disease. <u>Racial and Ethnic Differences in Treatment</u> • In black adults with hypertension but without HF or CKD, including those with

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	DM, initial antihypertensive treatment should include a thiazide-type diuretic or CCB. Two or more antihypertensive medications are recommended to achieve a BP target <130/80 mmHg in most adults with hypertension, especially in black adults with hypertension. Pregnancy • Women with hypertension who become pregnant, or are planning to become pregnant, should be transitioned to methyldopa, nifedipine, and/or labetalol during pregnancy. • Women with hypertension who become pregnant should not be treated with ACE inhibitors, ARBs, or direct renin inhibitors. Older Persons • Treatment of hypertension with an SBP treatment goal <130 mmHg is recommended for noninstitutionalized ambulatory community-dwelling adults (≥65 years of age) with an average SBP of ≥130 mmHg. • For older adults (≥65 years of age) with hypertension and a higher burden of comorbidity and limited life expectancy, clinical judgment, patient preference, and a team-based approach to assess risk/benefit is reasonable for decisions regarding intensity of BP lowering and choice of antihypertensive drugs. Hypertensive Crises • In adults with a hypertensive emergency, admission to an intensive care unit is recommended for continuous monitoring of BP and target organ damage and for parenteral administration of an appropriate agent. • For adults with a compelling condition (i.e., aortic dissection, severe pre-eclampsia or eclampsia, or pheochromocytoma crisis), SBP should be reduced to <140 mmHg during the first hour and to <120 mmHg in aortic dissection. • For adults without a compelling condition, SBP should be reduced by no more than 25% within the first hours; then, if stable, to 160/100 mmHg within the next two to six hours; and then cautiously to normal during the following 24 to 48 hours. Cognitive Decline and Dementia • In adults with hypertension, BP lowering is reasonable to prevent cognitive decline and dementia. Patients Undergoing Surgical Procedures • In patients with hypertension undergoing major surgery who have been on beta-blockers chronically, beta-blockers should be continued. • In patients with hypertension undergoing planned elective major surgery, it is reasonable to continue medical therapy for hypertension until surgery. • In patients with hypertension undergoing major surgery, discontinuation of ACE inhibitors or ARBs perioperatively may be considered. • In patients with planned elective major surgery and SBP ≥180 mmHg or DBP ≥110 mmHg, deferring surgery may be considered. • For patients undergoing surgery, abrupt pre-operative discontinuation of beta-blockers or clonidine is potentially harmful. • Beta-blockers should not be started on the day of surgery in beta-blocker-naïve patients. • Patients with intraoperative hypertension should be managed with IV medications until such time as oral medications can be resumed.
American Diabetes Association: **Standards of**	Hypertension/blood pressure control • Blood pressure should be measured at every routine visit. When possible, patients found to have elevated blood pressure (systolic blood pressure 120 to 129 mmHg

Clinical Guideline	Recommendation(s)
Medical Care in Diabetes (2023)[16]	and diastolic <80 mmHg) should have blood pressure confirmed using multiple readings, including measurements on a separate day, to diagnose hypertension. Patients with blood pressure ≥180/110 and cardiovascular disease could be diagnosed with hypertension at a single visit. • All hypertensive patients with diabetes should monitor their blood pressure at home. • For patients with diabetes and hypertension, blood pressure targets should be individualized through a shared decision-making process that addresses cardiovascular risk, potential adverse effects of antihypertensive medications, and patient preferences. • Individuals with diabetes and hypertension qualify for antihypertensive drug therapy when the blood pressure is persistently elevated ≥130/80 mmHg. The on-treatment target blood pressure goal is <130/80 mmHg, if it can be safely attained. • In pregnant patients with diabetes and preexisting hypertension, a blood pressure target of 110 to 135/85 is suggested in the interest of reducing the risk for accelerated maternal hypertension and minimizing impaired fetal growth. • For patients with blood pressure >120/80, lifestyle intervention consists of weight loss when indicated, a Dietary Approaches to Stop Hypertension (DASH)-style eating pattern including reducing sodium and increasing potassium intake, moderation of alcohol intake, and increased physical activity. • Patients with confirmed office-based blood pressure ≥130/80 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of pharmacologic therapy to achieve blood pressure goals. • Patients with confirmed office-based blood pressure ≥160/100 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of two drugs or a single pill combination of drugs demonstrated to reduce cardiovascular events in patients with diabetes. • Treatment for hypertension should include drug classes demonstrated to reduce cardiovascular events in patients with diabetes (ACE inhibitors, angiotensin receptor blockers, thiazide-like diuretics, or dihydropyridine calcium channel blockers). ACE inhibitors or angiotensin receptor blockers are recommended first-line therapy for hypertension in people with diabetes and coronary artery disease. • Multiple-drug therapy is generally required to achieve blood pressure targets (but not a combination of ACE inhibitors and angiotensin receptor blockers). • An ACE inhibitor or angiotensin receptor blocker, at the maximum tolerated dose indicated for blood pressure treatment, is the recommended first-line treatment for hypertension in patients with diabetes and urinary albumin–to–creatinine ratio ≥300 mg/g creatinine or 30 to 299 mg/g creatinine. If one class is not tolerated, the other should be substituted. • For patients treated with an ACE inhibitor, angiotensin receptor blocker, or diuretic, serum creatinine/estimated glomerular filtration rate and serum potassium levels should be monitored at least annually. • Patients with hypertension who are not meeting blood pressure targets on three classes of antihypertensive medications (including a diuretic) should be considered for mineralocorticoid receptor antagonist therapy. <u>Chronic kidney disease</u> • At least once a year, assess urinary albumin (e.g., spot urinary albumin–to–creatinine ratio) and estimated glomerular filtration rate in patients with type 1 diabetes with duration of five or more years and in all patients with type 2 diabetes. • In people with established diabetic kidney disease, urinary albumin (e.g., spot urinary albumin-to-creatinine ratio) and estimated glomerular filtration rate should be monitored one to four times per year depending on the stage of the disease. <u>Optimize glucose control to reduce the risk or slow the progression of chronic</u>

Clinical Guideline	Recommendation(s)
	kidney disease (CKD). • For patients with type 2 diabetes and diabetic kidney disease, use of a sodium-glucose cotransporter 2 inhibitor in patients with an estimated glomerular filtration rate ≥20 mL/min/1.73 m^2 and urinary albumin ≥200 mg/g creatinine is recommended to reduce CKD progression and cardiovascular events. • For patients with type 2 diabetes and diabetic kidney disease, use of a sodium–glucose cotransporter 2 inhibitor is recommended to reduce chronic kidney disease progression and cardiovascular events in patients with an estimated glomerular filtration rate ≥20 mL/min/1.73 m^2 and urinary albumin ranging from normal to 200 mg/g creatinine. • In people with type 2 diabetes and diabetic kidney disease, consider use of sodium–glucose cotransporter 2 inhibitors (if estimated glomerular filtration rate is ≥20 mL/min/1.73 m^2), a glucagon-like peptide 1 agonist, or a nonsteroidal mineralocorticoid receptor antagonist (if estimated glomerular filtration rate is ≥25 mL/min/1.73 m^2) additionally for cardiovascular risk reduction. • In people with chronic kidney disease and albuminuria who are at increased risk for cardiovascular events or chronic kidney disease progression, a nonsteroidal mineralocorticoid receptor antagonist shown to be effective in clinical trials is recommended to reduce chronic kidney disease progression and cardiovascular events. • Optimize blood pressure control and reduce blood pressure variability to reduce the risk or slow the progression of CKD. • Do not discontinue renin-angiotensin system blockade for minor increases in serum creatinine (≤30%) in the absence of volume depletion. • For people with nondialysis-dependent stage 3 or higher CKD, dietary protein intake should be a maximum of 0.8 g/kg body weight per day (the recommended daily allowance). For patients on dialysis, higher levels of dietary protein intake should be considered, since protein energy wasting is a major problem in some dialysis patients. • In nonpregnant patients with diabetes and hypertension, either an ACE inhibitor or an angiotensin receptor blocker is recommended for those with modestly elevated urinary albumin–to–creatinine ratio (30 to 299 mg/g creatinine) and is strongly recommended for those with urinary albumin–to–creatinine ratio ≥300 mg/g creatinine and/or estimated glomerular filtration rate <60 mL/min/1.73 m^2. • Periodically monitor serum creatinine and potassium levels for the development of increased creatinine and hyperkalemia when ACE inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists are used, or hypokalemia when diuretics are used. • An ACE inhibitor or an angiotensin receptor blocker is not recommended for the primary prevention of CKD in patients with diabetes who have normal blood pressure, normal urinary albumin–to–creatinine ratio (<30 mg/g creatinine), and normal estimated glomerular filtration rate. • Patients should be referred for evaluation by a nephrologist if they have continuously increasing urinary albumin levels and/or continuously decreasing estimated glomerular filtration rate and an estimated glomerular filtration rate <30 mL/min/1.73 m^2. • Promptly refer to a nephrologist for uncertainty about the etiology of kidney disease, difficult management issues, and rapidly progressing kidney disease.
American Association for the Study of Liver Diseases: **Diagnosis, Evaluation, and Management of**	<u>Treatment of ascites</u> • Moderate sodium restriction (2 g or 90 mmol/day) and diuretics (spironolactone with or without furosemide) are the first-line treatment in patients with cirrhosis and grade 2 ascites. • After ascites is adequately mobilized, attempts should be made to taper the diuretics to the lowest dose necessary to maintain minimal or no ascites to prevent the development of adverse effects.

Clinical Guideline	Recommendation(s)
Ascites, Spontaneous Bacterial Peritonitis and Hepatorenal Syndrome: 2021 Practice Guidance (2021)[17]	• Fluid restriction is not necessary unless serum sodium is <125 mmol/L. • In patients receiving diuretics, body weight and serum creatinine and sodium should be regularly monitored to assess response and to detect the development of adverse effects. • Human albumin solution (20 to 40 g/week) or baclofen administration (10 mg/day, with a weekly increase of 10 mg/day, up to 30 mg/day) can be considered in cases of severe muscle cramps. • Large-volume paracentesis is the first-line treatment of grade 3 ascites. After paracentesis, sodium restriction and diuretics should be started. • Referral for liver transplant evaluation should be considered in patients with grade 2 or 3 ascites. • Nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers should be avoided in patients with cirrhosis and ascites. • Aminoglycosides should be avoided whenever possible in the treatment of bacterial infections. • For patients with cirrhosis and diuretic-responsive ascites, controversial data suggest potential benefits of long-term infusion of human albumin solution. At present, no recommendation can be made for its use in routine clinical practice.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the thiazide diuretics are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Thiazide Diuretics[1-4]

Indication	Chlorothiazide*	HCTZ*
Edema		
Adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, and corticosteroid and estrogen therapy	✔	✔ (tablet)
Hypertension		
Treatment of hypertension	✔ † (oral)	✔ †

*Has been found useful in edema due to various forms of renal dysfunction such as nephrotic syndrome, acute glomerulonephritis, and chronic renal failure.
†Alone or in combination with other antihypertensive agents.
HCTZ=hydrochlorothiazide

IV. Pharmacokinetics

The pharmacokinetic parameters of the thiazide diuretics are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Thiazide Diuretics[4]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life
Chlorothiazide	Poor	Not reported	Not metabolized	Renal (96)	45 to 120 minutes
HCTZ	60 to 80	40	Not metabolized	Renal (50 to 70)	10 to 12 hours

HCTZ=hydrochlorothiazide

V. Drug Interactions

Major drug interactions with the thiazide diuretics are listed in Table 5.

Table 5. Major Drug Interactions with the Thiazide Diuretics[4]

Generic Name(s)	Interaction	Mechanism
Thiazide diuretics (chlorothiazide, HCTZ)	Amphetamines	Concurrent use of amphetamines and thiazide diuretics may result in increased exposure to amphetamine.
Thiazide diuretics (chlorothiazide, HCTZ)	Digitalis glycosides	Thiazide diuretics may induce electrolyte disturbances which may predispose patients to digitalis-induced arrhythmias.
Thiazide diuretics (chlorothiazide, HCTZ)	Dofetilide	Thiazide diuretics may induce hypokalemia which may increase the risk of torsades de pointes.
Thiazide diuretics (chlorothiazide, HCTZ)	Lithium	Thiazide diuretics may promote enhanced proximal tubular reabsorption of lithium leading to elevated serum concentrations. Thiazide diuretics may increase the therapeutic and toxic effects of lithium.
Thiazide diuretics (chlorothiazide, HCTZ)	Loop diuretics	Both groups have synergistic effects that may result in profound diuresis and serious electrolyte abnormalities
Thiazide diuretics (chlorothiazide, HCTZ)	NSAIDs	Concurrent use of NSAIDs and thiazide diuretics may result in reduced diuretic effectiveness and possible nephrotoxicity.
Thiazide diuretics (chlorothiazide)	Bepridil	Concurrent use of chlorothiazide and bepridil may result in hypokalemia and subsequent cardiotoxicity (torsades de pointes).
Chlorothiazide	Flecainide	Concurrent use of chlorothiazide and flecainide may result in increased risk of electrolyte imbalance and subsequent cardiotoxicity.
Hydrochlorothiazide	Methotrexate	Concurrent use of hydrochlorothiazide and methotrexate may result in increased methotrexate exposure and enhanced myelosuppression.

HCTZ=hydrochlorothiazide, NSAIDS=nonsteroidal anti-inflammatory drugs

VI. Adverse Drug Events

The most common adverse drug events reported with the thiazide diuretics are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Thiazide Diuretics[1-4]

Adverse Events	Chlorothiazide	HCTZ
Cardiovascular		
Hypotension	✔	✔
Necrotizing angiitis	✔	✔
Orthostatic hypotension	✔	✔
Central Nervous System		
Dizziness	✔	✔
Fever	✔	✔
Headache	✔	✔
Restlessness	✔	✔
Vertigo	✔	✔
Dermatological		
Alopecia	✔	✔
Cutaneous vasculitis	-	✔
Erythema multiforme	✔	✔
Exfoliative dermatitis	✔	✔
Photosensitivity	✔	✔
Purpura	✔	✔

Adverse Events	Chlorothiazide	HCTZ
Rash	✔	✔
Stevens-Johnson syndrome	✔	✔
Toxic epidermal necrolysis	✔	✔
Urticaria	✔	✔
Vasculitis	-	✔
Gastrointestinal		
Abdominal cramping	✔	✔
Anorexia	✔	✔
Constipation	✔	✔
Diarrhea	✔	✔
Gastric irritation	✔	✔
Nausea	✔	✔
Pancreatitis	✔	✔
Sialadenitis	✔	✔
Vomiting	✔	✔
Genitourinary		
Impotence	✔	✔
Hematologic		
Agranulocytosis	✔	✔
Aplastic anemia	✔	✔
Hemolytic anemia	✔	✔
Leukopenia	✔	✔
Thrombocytopenia	✔	✔
Hepatic		
Jaundice	✔	✔
Laboratory Test Abnormalities		
Cholesterol increased	✔	-
Electrolyte imbalance	✔	✔
Hypercalcemia	-	✔
Hyperglycemia	✔	✔
Hyperuricemia	✔	✔
Hypochloremic alkalosis	✔	-
Hypokalemia	✔	-
Hypomagnesemia	✔	-
Hyponatremia	✔	-
Triglycerides increased	✔	-
Musculoskeletal		
Muscle spasm	✔	✔
Paresthesia	✔	✔
Weakness	✔	✔
Ocular		
Blurred vision	✔	✔
Xanthopsia	✔	✔
Renal		
Glycosuria	✔	✔
Interstitial nephritis	✔	✔
Renal dysfunction	✔	✔
Renal failure	✔	✔
Respiratory		
Pneumonitis	✔	✔
Pulmonary edema	✔	✔
Respiratory distress	✔	✔
Other		
Anaphylactic reactions	✔	✔

Adverse Events	Chlorothiazide	HCTZ
Systemic lupus erythematosus	✔	-

✔ Percent not specified
-Event not reported
HCTZ=hydrochlorothiazide

VII. Dosing and Administration

The usual dosing regimens for the thiazide diuretics are listed in Table 7.

Table 7. Usual Dosing Regimens for the Thiazide Diuretics[1-5]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Chlorothiazide	Edema: Injection, suspension: 0.5 to 1 g once or twice daily, often administered on alternate days or on three to five days each week Hypertension: Injection, suspension: initial, 0.5 or 1 g/day as a single dose or in divided dose(s); maintenance, adjust according to blood pressure response, some patients may require up to 2 g/day in divided doses	Diuresis and hypertension: Suspension: the usual pediatric dosage is 5 to 10 mg per pound (10 to 20 mg/kg) per day in single or two divided doses, not to exceed 375 mg per day in infants up to 2 years of age or 1 g per day in children 2 to 12 years of age. In infants less than 6 months of age, doses up to 15 mg per pound (30 mg/kg) per day in two divided doses may be required	Injection: 500 mg Suspension 250 mg/5 mL
HCTZ	Edema: Capsule, tablet: maintenance, 25 to 100 mg/day in a single or divided dose(s) Hypertension: Capsule, tablet: initial, 12.5 to 25 mg once daily; maintenance, 50 to 100 mg daily in a single or divided dose(s)	Diuresis and hypertension: Tablet: the usual pediatric dosage is 0.5 to 1 mg per pound (1 to 2 mg/kg) per day in single or two divided doses, not to exceed 37.5 mg per day in infants up to 2 years of age or 100 mg per day in children 2 to 12 years of age. In infants less than 6 months of age, doses up to 1.5 mg per pound (3 mg/kg) per day in two divided doses may be required.	Capsule: 12.5 mg Tablet: 12.5 mg 25 mg 50 mg

HCTZ=hydrochlorothiazide

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the thiazide diuretics are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Thiazide Diuretics

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Edema				
Rengo et al.[18] (1979) HCTZ 150 mg QD vs amiloride 15 mg QD vs amiloride and HCTZ 15-150 mg QD (fixed-dose combination product)	RCT Patients 35 to 60 years of age with liver cirrhosis and ascites or CHF	N=30 15 days	Primary: Body weight, 24 hour diuresis, serum sodium, serum potassium, sodium and potassium urinary loss Secondary: Not reported	Primary: All treatment groups had a significant reduction in body weight from baseline (P<0.001 for all). Amiloride and HCTZ-treated patients achieved a significantly greater reduction compared to amiloride-treated patients (P<0.001). All treatment groups significantly differed from baseline in 24 hour diuresis (P<0.01). Amiloride and HCTZ- and HCTZ-treated patients achieved greater diuresis compared to amiloride-treated patients (P<0.001 for both). Serum sodium was reduced from baseline in all treatment groups. HCTZ-treated patients had a significantly greater reduction than amiloride- (P<0.01) and amiloride and HCTZ-treated patients (P<0.001). Sodium urinary loss was seen with all treatments at day two, amiloride and HCTZ therapy had maintained the loss at day five (P<0.001 for both). Serum potassium decreased in HCTZ-treated patients but increased in amiloride- and amiloride and HCTZ-treated patients. HCTZ-treated patients had a marked increase in potassium urinary loss (P<0.001). Secondary: Not reported
Cheitlin et al.[19] (1991) Amiloride 5 or 10 mg QD for 7 days, followed by placebo plus HCTZ 50 or 100	DB, PC, RCT, XO Patients with a history CHF and ≥1 episode of pulmonary edema (NYHA class 2 to 3) who were not	N=11 21 days	Primary: Hemodynamic changes at rest and exercise Secondary: Not reported	Primary: At rest, there were no significant differences between placebo- and amiloride-treated patients in right atrial pressure, pulmonary atrial pressure, heart rate, pulmonary artery wedge pressure, systemic arterial pressure, right ventricular stroke work index, left ventricular stroke work index, systemic vascular resistance, cardiac index or stroke volume index (P values not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg QD for 14 days vs placebo for 14 days, followed by amiloride 5 or 10 mg plus HCTZ 50 or 100 mg QD for the next 7 days	previously treated			During exercise, there were significant differences between placebo- and amiloride-treated patients at the 50-watt stage in right atrial pressure (15.0 vs 10.5 mm Hg), pulmonary artery wedge pressure (28.6 vs 22.1 mm Hg), pulmonary artery diastolic pressure (32.2 vs 21.6 mm Hg), mean pulmonary artery pressure (44.4 vs 38.9 mm Hg), left ventricular stroke work index (69.5 vs 77.9 g-m/m^2) and stroke volume index (44.9 vs 46.2 cc/beat/m^2), respectively (P values not reported). There were no significant differences between placebo and amiloride therapy during exercise in right ventricular stroke work index, heart rate, aortic pressure, cardiac index and total systemic vascular resistance (P values not reported). Secondary: Not reported
Kohvakka[20] (1988) HCTZ 50 mg BID vs amiloride 5 mg BID plus HCTZ 50 mg BID vs triamterene 75 mg BID plus HCTZ 50 mg BID vs KCl 1,000 mg BID plus HCTZ 50 mg BID	RCT, XO Patients 41 to 69 years of age with CHF (NYHA class 2 to 3) who developed persistent hypokalemia on HCTZ alone	N=25 5 months	Primary: Changes in weight, blood pressure, serum sodium, serum potassium and total body potassium Secondary: Percentage with hypokalemia, median days until hypokalemia detection, serum magnesium	Primary: Weight loss was significant in amiloride plus HCTZ- and triamterene plus HCTZ-treated patients (P=0.05 for both), but not in KCl plus HCTZ-treated patients (P value not reported), compared to HCTZ-treated patients. No significant changes in blood pressure were observed (P values not reported). No differences in serum sodium were observed in amiloride plus HCTZ- or triamterene plus HCTZ-treated patients (P values not reported). Serum sodium levels were slightly higher in KCl plus HCTZ-patients compared to HCTZ-treated patients (P=0.01). Serum potassium was found to be significantly higher in all combination treated-patients compared to HCTZ-treated patients (P=0.01 for all comparisons). Total body potassium was significantly higher in amiloride plus HCTZ- and triamterene plus HCTZ-treated patients (P=0.05 for both), but not in KCl plus HCTZ-treated patients (P value not reported), compared to HCTZ-treated patients. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The percentages of patients that became hypokalemic were 39, 52 and 52% in amiloride plus HCTZ-, triamterene plus HCTZ- and KCl plus HCTZ-treated patients (P values not reported). The median days until hypokalemia detection were 114.0, 75.0 and 51.5 for amiloride plus HCTZ-, triamterene plus HCTZ- and KCl plus HCTZ-treated patients (P values not reported). Serum magnesium was maintained at a significantly higher rate in amiloride plus HCTZ- and triamterene plus HCTZ- patients compared to KCl plus HCTZ-treated patients (P values not reported).
Faris et al.[21] (2006) Thiazide diuretics (chlorothiazide), loop diuretics (furosemide, bumetanide), or potassium-sparing diuretics (amiloride, triamterene) vs placebo or active control (ACE inhibitors, digoxin)	MA (14 trials) Adult patients with chronic heart failure	N=525 2 to 52 weeks	Primary: Mortality Secondary: Effect of diuretic withdrawal on worsening of heart failure and exercise capacity	Primary: Pooled data from three PC trials (n=202) reporting on mortality revealed that mortality was lower for diuretic-treated patients compared to placebo-treated patients (2.7 vs 10.9%, respectively; OR, 0.24; 95% CI, 0.07 to 0.83; P=0.02). The difference represents an absolute risk reduction of 8% in mortality in diuretic-treated patients (NNT, 12.5). Secondary: Pooled data from two PC trials (n=169) reporting on the effect of diuretics on worsening heart failure revealed lower admission rates for worsening heart failure in diuretic-treated patients compared to placebo-treated patients (OR, 0.07; 95% CI, 0.01 to 0.52; P=0.01). Pooled data from two parallel RCTs (n=43) reporting on the effect of diuretics on exercise capacity revealed that diuretic therapy improved exercise capacity compared to active control (WMD, 0.74; 95% CI, 0.37 to 1.11; P<0.0001). Pooled data from two XO RCTs (n=48) revealed similar results (WMD, 0.67; 95% CI, 0.02 to 1.31; P=0.04). In total (n=91), diuretic therapy improved exercise capacity in patients with chronic heart failure (WMD, 0.72; 95% CI, 0.40 to 1.04; P<0.0001).
Hypertension				
Hua et al.[22] (1976) Chlorothiazide up to 5 g BID	XO Patients with HTN	N=20 Duration not specified	Primary: Blood pressure, serum potassium Secondary:	Primary: Blood pressures on metolazone tended to be lower than on chlorothiazide, but the difference was not statistically significant. Both agents significantly lowered serum potassium concentrations and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs metolazone 5 mg QD			Not reported	total body potassium to a similar degree. However, the serum potassium did not fall below the normal range in any patient and no potassium supplements were required. Secondary: Not reported
Carter et al.[23] (2004) HCTZ 12.5 to 450 mg/day vs chlorthalidone 12.5 to 600 mg/day	MA Included trials which evaluate the pharmacokinetic and blood pressure lowering effects of chlorthalidone and HCTZ	N=200 Duration varied per study	Primary: Blood pressure Secondary: Serum potassium	Primary: In a dose equivalence study comparing HCTZ 100 mg QD to chlorthalidone 50 mg QD, blood pressure (SBP/DBP) reduced by 18/8 and 25/10 mm Hg compared to baseline, respectively. In another study comparing HCTZ 25 mg and triamterene 50 mg QD, HCTZ 50 mg and triamterene 100 mg QD, and chlorthalidone 50 mg QD, the blood pressure reduction was 15/8, 18/12, and 25/16 mm Hg, respectively. One other dose equivalence study comparing HCTZ 50 mg BID and chlorthalidone 50 mg QD, blood pressure reduction was 22/16 and 18/15 mm Hg, respectively. All available studies were inspected and it was concluded that HCTZ 50 mg is approximately equivalent to chlorthalidone 25 to 37 mg. Furthermore, it was suggested that chlorthalidone doses should generally be approximately 50% to 75% of the typical HCTZ dose. Secondary: In a study comparing HCTZ 100 mg QD and chlorthalidone 50 mg QD, potassium increased slightly with chlorthalidone (0.02 mEq/L) and decreased significantly with HCTZ (0.22 mEq/L; P=0.009). However, in another study comparing HCTZ 50 mg BID and chlorthalidone 50 mg QD, serum potassium decreased by 0.38 mEq/L with HCTZ and by 0.03 mEq/L with chlorthalidone. The difference was not statistically significant (P<0.07).
Ernst et al.[24] (2006)	RCT, SB, XO Men and women	N=30 8 weeks plus 4	Primary: Comparison of the change in 24-hour	Primary: At week eight, there was a greater reduction in 24-hr mean SBP with chlorthalidone 25 mg/day compared to HCTZ 50 mg/day compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
HCTZ 25 mg in the morning vs chlorthalidone 12.5 mg in the morning At week 4, both HCTZ and chlorthalidone were titrated to 50 mg in the morning and 25 mg in the morning, respectively for the remainder of the trial.	aged 18 to 79 years with pre-HTN or a new or established diagnosis of HTN (stage 1 or 2), not receiving antihypertensive medications, and had an average office blood pressure value in the last 6 months between 140 and 179 mm Hg systolic or 90 and 109 mm Hg diastolic	week washout period	mean SBP and DBP from baseline to week 8 Secondary: Comparison of changes in mean SBP and mean DBP for office blood pressure at each visit, change in ambulatory daytime and nighttime mean SBP and DBP from baseline to week 8, development of hypokalemia	baseline (-12.4±1.8 vs -7.4±1.7 mm Hg, respectively; P=0.054). Secondary: There was a trend in favor of greater reduction in SBP with chlorthalidone than with HCTZ at each office visit. However, the difference was only statistically significant at week 2 (-15.7±2.2 vs -4.5±2.1 mm Hg, respectively; P=0.001). Although mean reductions in DBP was also greater with chlorthalidone compared to HCTZ at each study visit, the differences were not statistically significant at any visit (P>0.89 for all). The reduction in SBP during nighttime hours was -13.5±1.9 mm Hg for chlorthalidone and -6.4±1.7 mm Hg for HCTZ (P=0.009). The reduction in daytime mean SBP between both groups was not significantly different (-11.4±2.0 vs -8.1±1.9 mm Hg, respectively; P=0.230). Changes in serum potassium were similar between treatment groups (P=0.76). The incidence of hypokalemia was 50% in patients taking HCTZ and 46% in patients taking chlorthalidone (P=0.682).
Finnerty et al.[25] (1980) HCTZ 50 mg plus reserpine 0.125 mg vs chlorthalidone 50 mg plus reserpine 0.25 mg	DB Patients with essential HTN unresponsive to diet control and diuretic therapy	N=57 6 weeks	Primary: The change in mean DBP from baseline Secondary: Incidence of frequent or severe side effects	Primary: The chlorthalidone plus reserpine group had a mean decrease in DBP of 17.0 mm Hg at study endpoint compared with a mean decrease of 18.6 mm Hg in the HCTZ plus reserpine group. At study completion both treatment groups achieved diastolic control of at least 5 mm Hg below the targeted diastolic goal of 90 mm Hg. Secondary: There were no reports of frequent or severe side effects in either treatment group.
Bakris et al.[26] (2012) Azilsartan medoxomil and chlorthalidone	DB, RCT Patients aged ≥18 years with stage 2 primary HTN	N=609 10 weeks (after 2 week placebo run-in)	Primary: Change in trough, seated clinic systolic blood pressure at weeks 6 and 10	Primary: Change in SBP at week six demonstrated a mean difference of -5.6 mm Hg (95% CI, -8.3 to -2.9; P<0.001) in favor of the chlorthalidone group. Fewer patients in the chlorthalidone group required titration to a higher dose of diuretic (P<0.001). At the end of week 10, a greater mean SBP reduction was maintained in the chlorthalidone group compared to the

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(single pill) vs azilsartan medoxomil and HCTZ (co-administered) Treatments were titrated to a target of <140/90 mm Hg (or <130/80 mm Hg if diabetes of chronic kidney disease)			Secondary: Change from baseline in clinic DBP and 24-hour mean systolic and diastolic blood pressures by ambulatory blood pressure monitoring	HCTZ group (-5.0 mm Hg; 95% CI, -7.5 to -2.5; P<0.001). Secondary: The chlorthalidone group demonstrated a significantly greater reduction in 24-hour mean SBP at weeks six and 10. For both clinica and 24-hour mean DBP, greater blood pressure reduction was observed in the chlorthalidone group compared to the HCTZ group at both study points.
Valmin et al.[27] (1975) HCTZ 12.5 mg BID vs furosemide 12.5, 25, or 40 mg BID vs placebo	DB, RCT, XO, 5 experimental periods each of 4 weeks Men and women with essential HTN	N=34 20 weeks	Primary: Blood pressure, urinary output, serum electrolytes, safety and tolerability Secondary: Not reported	Primary: When compared to placebo, there was a significant reduction of blood pressure with HCTZ 12.5 mg BID and furosemide 12.5 mg BID (P<0.05). Paired comparison showed that HCTZ 12.5 mg BID and furosemide 25 and 40 mg BID had a similar hypotensive effect, irrespective of the initial blood pressure (P>0.10). When compared to placebo, the urinary output increased significantly with furosemide 12.5, 25, or 40 mg BID (P<0.05, P<0.01 and P<0.001, respectively) but not with the HCTZ group (P>0.10). Sodium level did not alter during the various treatment periods when compared with the placebo period, or between the individual treatment periods (P>0.10). Potassium level fell significantly during the HCTZ period (P<0.001) and furosemide 25 mg and 40 mg BID period (P<0.01 and P<0.001, respectively). Potassium level was not significantly affected with furosemide 12.5 mg BID (P>0.10).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Araoye et al.[28] (1978) HCTZ 50 mg BID vs furosemide 40 mg BID	DB, XO Patients with HTN	N=not specified 3 months	Primary: Blood Pressure Secondary: Not reported	Primary: Furosemide and HCTZ significantly reduced blood pressure. The decrease in blood pressure was consistently greater in the HCTZ group than with furosemide; however the difference was significant in regards to SBP only. Secondary: Not reported
Madkour et al.[29] (1996) HCTZ 50 mg QD vs indapamide 2.5 mg QD	RCT Patients aged 32 to 70 years with impaired renal function for 1 to 15 years and moderate HTN for 2 to 27 years, initial creatinine clearance between 32 and 80 mL/min/1.73 m^2 BSA	N=28 24 months	Primary: Blood pressure, changes in creatinine clearance Secondary: Not reported	Primary: Blood pressure normalized in all patients taking either indapamide or HCTZ. There were no significant differences in SBP or DBP between groups. At 24 months, creatinine clearance progressively increased from 58±4.4 to 72±4.4 mL/min/1.73 m^2 BSA in patients treated with indapamide ($P<0.01$). Creatinine clearance progressively decreased from 65±3.0 to 53±3.0 mL/min/1.73 m^2 BSA in patients treated with HCTZ ($P<0.01$). Creatinine clearance significantly increased by 28.5±4.4% with indapamide and decreased by 17.4±3.0% with thiazide therapy ($P<0.01$). Secondary: Not reported
Ames[30] (1996) HCTZ ≤25 mg (or its equivalent in other thiazides) up to 112.5 mg QD vs	MA (13 trials) Patients with HTN	N=1,547 1 to 25 months	Primary: Comparison of the effects of thiazides and indapamide on blood lipids and blood pressure Secondary: Not reported	Primary: The mean change from baseline was 1.4% for TC, 5.5% for HDL-C, and -0.5% for TG with indapamide. None of the differences were statistically significant. Low-dose thiazide therapy did not decrease TC at any data point. The mean percent increase in TC was 3.8%, in HDL-C was 3.1%, and in TG was 10.8% with low-dose HCTZ. The increases in TC and TG from baseline was statistically significant ($P<0.01$).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
indapamide 2.5 mg QD				The mean change in TC was 6.3%, in HDL-C was -0.5%, and in TGs was 19.5% for higher doses of HCTZ. Increases from baseline in TC and TG were statistically significant. SBP decreased more with higher doses of HCTZ than with low-dose thiazide therapy (P<0.05). The effects of indapamide on systolic arterial pressure were intermediate between, and not statistically different from, either thiazide dose. Decreases in DBP did not differ among groups. Secondary: Not reported
Larochelle et al.[31] (1985) HCTZ 50 mg vs amiloride 5 mg/day and HCTZ 50 mg/day	DB, RCT Ambulant patients 18 to 70 years of age with essential HTN who after not being treated for ≥2 weeks prior to the trial had a supine DBP of 95 to 109 mm Hg and a serum potassium level of >3.5 mmol/L	N=266 8 weeks	Primary: Blood pressure, serum potassium concentration Secondary: Not reported	Primary: At eight weeks, there were no differences between the two treatments in the mean blood pressure reductions (P value not reported). During the eight weeks of treatment, the HCTZ plus amiloride-treated patients experienced a decrease in mean supine blood pressure (159/99 to 138/88 mm Hg) and serum potassium levels (4.23 to 3.91 mmol/L) (P values not reported). During the eight weeks of treatment, HCTZ-treated patients experienced a reduction in mean supine blood pressure (157/99 to 138/87 mm Hg) and serum potassium levels (4.16 to 3.69 mmol/L) (P values not reported). Hypokalemia occurred less frequently in HCTZ plus amiloride-treated patients compared to HCTZ-treated patients (14 and 29%, respectively; P=0.0026). However, the proportions of patients with a potassium level exceeding 4.5 mmol/L were similar (4.5 vs 3.9%, respectively; P value not reported). Secondary: Not reported
Salmela et al.[32] (1986) HCTZ 25 mg daily	DB, MC, PG, RCT Adult patients with mild to moderate HTN	N=40 12 weeks	Primary: Changes in blood pressure Secondary:	Primary: At the end of the first treatment period (four weeks), mean supine SBP and DBP was 161 and 91 mm Hg in amiloride plus HCTZ-treated patients (P<0.01 and P<0.001, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs amiloride 2.5 mg/day and HCTZ 25 mg/day			Not reported	At the end of the first treatment period (four weeks), mean supine SBP and DBP was 165 and 96 mm Hg in HCTZ-treated patients (P<0.01 for both). At the end of the second treatment period (eight weeks), mean supine SBP and DBP was 154 and 86 mm Hg in amiloride plus HCTZ-treated patients (P<0.01 and P<0.001). At the end of the second treatment period (eight weeks), mean supine SBP and DBP was 155 and 90 mm Hg in HCTZ-treated patients (P<0.001 and P<0.001). There were no significant differences in blood pressure reduction between the two treatments (P value not reported). Secondary: Not reported
Multicenter Diuretic Cooperative Study Group[33] (1981) HCTZ 50 mg QD vs amiloride and HCTZ 5-50 mg QD (fixed-dose combination product) vs amiloride 5 mg QD	DB, MC, RCT Patients 21 to 69 years of age with mild to moderate essential HTN (supine DBP 95 to 115 mm Hg)	N=179 12 weeks	Primary: Change from baseline in average supine SBP and DBP Secondary: Heart rate, body weight, serum potassium	Primary: Baseline vs 12 week average supine blood pressure was 153/101 vs 139/93 for amiloride-, 160/100 vs 137/90 for amiloride and HCTZ- and 154/101 vs 134/89 mm Hg for HCTZ-treated patients. Reductions in supine blood pressure were significant with all treatments (P<0.01). The SBP reduction was significantly greater with amiloride and HCTZ-treated patients compared to amiloride-treated patients at all weeks and HCTZ-treated patients at four and eight weeks (P<0.05, both). Secondary: No significant changes from baseline in heart rate were observed in amiloride and HCTZ-treated patients (P values not reported). An increase in heart rate of 3.3 bpm was observed in these patients (P<0.05). Changes in body weight from baseline were -1.17 kg in amiloride and HCTZ-, -0.72 kg in HCTZ- and 0.045 kg in amiloride-treated patients (P<0.05, for amiloride plus HCTZ only). Changes in serum potassium from baseline were 0.23 in amiloride- (P<0.01), -0.38 in amiloride and HCTZ- (P<0.01) and -0.59 mEq/L in HCTZ-treated patients (P<0.01). The change in HCTZ-treated patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				was statistically greater than the change in the amiloride and HCTZ-treated patients (P<0.05). Twenty three, two and zero percent of HCTZ-, amiloride and HCTZ- and amiloride-treated patients experienced hypokalemia.
Wray et al.[34] (2010) HCTZ 12.5 to 50 mg QD vs spironolactone 25 to 100 mg QD Patients also received potassium 0 to 40 mEq to maintain blinding.	DB, RCT Patients ≥60 years of age with stage 1 HTN	N=36 6 months	Primary: Blood pressure, sympathetic nervous system activity Secondary: Not reported	Primary: Arterial blood pressure decreased significantly with spironolactone (SBP: 160 to 134 mm Hg and DBP: 77 to 68 mm Hg) and with HCTZ (SBP: 161 to 145 mm Hg and 78 to 73 mm Hg). There was no significant difference between the groups. Sympathetic nervous system activity was significantly reduced after spironolactone (plasma norepinephrine: 378 to 335 pg/mL; P=0.04; [3H]-norepinephrine release rate: 2.74 to 1.97 μg/min/m^2; P=0.04), but not with HCTZ (plasma norepinephrine: 368 to 349 pg/mL; P=0.47; [3H]-norepinephrine release rate: 2.63 to 2.11 μg/min/m^2; P=0.21). There were no instances of hyperkalemia, and no other adverse effects were reported. Secondary: Not reported
Nash et al.[35] (1977) HCTZ 50 mg BID vs spironolactone 50 mg BID vs spironolactone 100 mg BID vs	DB, RCT Male outpatients between the ages of 21 to 65 years, with essential HTN, DBP between 90 to 114 mm Hg	N=79 12 weeks	Primary: Change in SBP, DBP, blood urea nitrogen, serum potassium, gynecomastia Secondary: Not reported	Primary: At week 12, all study groups exhibited significant reductions in SBP and DBP from baseline (P<0.05). At week 12, all three spironolactone monotherapy groups exhibited statistically significant increases in blood urea nitrogen from baseline (P<0.05). At week 12, the HCTZ monotherapy group was associated with a statistically significant decrease in serum potassium levels (P<0.001). At week 12, all three spironolactone monotherapy groups exhibited statistically significant increases in serum potassium levels from baseline (P<0.05). At week 12, the spironolactone and HCTZ combination group was not

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
spironolactone 200 mg BID vs spironolactone and HCTZ 25-25 mg BID (fixed-dose combination product)				associated with statistically significant increases in serum potassium levels from baseline. A dose-related risk of gynecomastia was observed in the spironolactone-treated patients. Among patients treated with spironolactone 50, 100, or 200 mg BID; 5.5, 11.8, and 40% reported gynecomastia symptoms. Of the patients randomized to spironolactone and HCTZ combination product, 7.7% reported gynecomastia symptoms. Secondary: Not reported
Schrijver et al.[36] (1979) Spironolactone 50 mg BID for 8 weeks (single drug phase), with the addition of a placebo for subsequent 4 weeks (group IA) vs spironolactone 50 mg BID for 8 weeks (single drug phase), subsequently HCTZ 50 mg BID was added to the regimen for an additional 4 weeks (group IB) vs	DB Patients, between 24 to 63 years of age, with DBP between 90 to 114 mm Hg	N=49 20 weeks (4-week placebo run-in, 8-week single drug therapy, 4-week two-drug therapy, 4-week recovery)	Primary: Change in MABP, serum potassium, uric acid level, blood glucose, blood urea nitrogen, creatinine, plasma renin activity, aldosterone, side effects Secondary: Not reported	Primary: Following eight weeks of therapy with a single drug, all study groups exhibited a statistically significant reduction in MABP from baseline (P<0.01). There were no significant differences in MABP reduction among the study groups. The addition of a second drug to the antihypertensive regimen was not associated with a significant improvement in MABP. At the end of the two-drug treatment period, there were no differences in MABP among any of the study groups. Spironolactone therapy was associated with a significant decrease in serum potassium concentration from baseline (P<0.001). Spironolactone regimens were not associated with a significant change in potassium levels from baseline. Following eight weeks of therapy with a single drug, HCTZ-treated patients experienced a statistically significant increase in uric acid from baseline (P<0.001). Groups IIA and IIB also experienced a significant but smaller increase in uric acid level from baseline (P<0.05) with no change in groups I and IV. During the single-drug treatment phase, patients randomized to group I experienced a significant increase in blood glucose from baseline (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
spironolactone 100 mg BID for 8 weeks (single drug phase), with the addition of a placebo for subsequent 4 weeks (group IIA) vs spironolactone 100 mg BID for 8 weeks (single drug phase), subsequently HCTZ 50 mg BID was added to the regimen for an additional 4 weeks (group IIB) vs spironolactone 200 mg BID for 8 weeks (single drug phase), with the addition of a placebo for subsequent 4 weeks (group IIIA) vs spironolactone 200				During the single-drug treatment phase, all patients except those randomized to group I experienced a significant increase in blood urea nitrogen from baseline (P<0.05). During the single-drug treatment phase, patients randomized to groups I and II experienced a significant increase in serum creatinine from baseline (P<0.05). During the single-drug treatment phase, all treatment groups experienced a significant increase in plasma renin activity from baseline (P<0.01). The addition of HCTZ in the two-drug study phase was associated with a rise in plasma renin activity in all study groups (P<0.05). All treatment groups experienced a significant increase in plasma aldosterone from baseline (P<0.05). Gynecomastia was reported only by patients randomized to the higher-dose spironolactone groups. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg BID for 8 weeks (single drug phase), subsequently HCTZ 50 mg BID was added to the regimen for an additional 4 weeks (group IIIB) vs HCTZ 50 mg BID for 8 weeks (single drug phase), with the addition of a placebo for subsequent 4 weeks (group IVA) vs HCTZ 50 mg BID for 8 weeks (single drug phase), subsequently HCTZ 50 mg BID was added to the regimen for an additional 4 weeks (group IVB)				
Johnson et al.[37] (2009) HCTZ 12.5 to 25 mg QD for 9	RCT Patients 17 to 65 years of age mild to moderate essential	N=368 15 to 18 weeks	Primary: Blood pressure lowering effect of drug initiation order: the addition	Primary: When analyzed by order of initiation of the two drugs, the response to HCTZ and atenolol was greater overall than that seen for atenolol and HCTZ (P=0.0007 and P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
weeks, followed by HCTZ 12.5 to 25 mg QD and atenolol 50 to 100 mg QD for 9 weeks vs atenolol 50 to 100 mg QD for 9 weeks, followed by atenolol 50 to 100 mg QD and HCTZ 12.5 to 25 mg QD for 9 weeks	HTN		of a β-blocker to a thiazide versus the addition of a thiazide to a β-blocker Secondary: Not reported	This study suggests that initiation of HCTZ followed by atenolol results in greater blood pressure lowering as compared with initiation in the reverse order, with differences that are potentially clinically important. Secondary: Not reported
Dahlöf et al.[38] (1991) Hypertension (STOP) Atenolol 50 mg QD, HCTZ 25 mg QD plus amiloride 2.5 mg QD, metoprolol 100 mg QD, or pindolol 5 mg QD vs placebo	DB, MC, RCT Swedish men and women 70 to 84 years old with treated or untreated essential HTN defined as SBP ≥180 mm Hg with a DBP of ≥90 mm Hg, or DBP >105 mm Hg irrespective of the SBP measured on 3 separate occasions during a 1-month placebo run-in phase in previously untreated patients	N=1,627 25 months	Primary: Frequency of stroke, MI, and other cardiovascular death Secondary: Not reported	Primary: The active treatments significantly reduced the number of all primary endpoints (94 vs 58; RR, 0.60; 95% CI, 0.43 to 0.85; P=0.0031), frequency of stroke (53 vs 29; RR, 0.53; 95% CI, 0.33 to 0.86; P=0.0081) and frequency of other cardiovascular deaths (13 vs 4; RR, 0.30; 95% CI, 0.07 to 0.97) compared to placebo. There was not a statistically significant decrease observed in the rate of MI between the active treatments and placebo (28 vs 25; RR, 0.87; 95% CI, 0.49 to 1.56). Secondary: Not reported
Frishman et al.[39]	DB, MC, PC, RCT	N=512	Primary:	Primary:

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(1994) HCTZ 6.25 or 25 mg QD vs bisoprolol 2, 5, 10, or 40 mg QD vs bisoprolol plus HCTZ, all possible combinations	Patients 21 years and older with mild to moderate essential HTN whose weight was 35% of the ideal for height and frame and mean sitting DBP was stable and between 95 to 115 mm Hg	12 weeks	Changes in DBP and SBP Secondary: Not reported	All treatment groups (all doses) of bisoprolol, HCTZ and the combination of bisoprolol and HCTZ significantly reduced sitting DBP from baseline (P<0.01). The reduction in blood pressure was significantly greater as the doses of the bisoprolol, HCTZ and the combination of bisoprolol-HCTZ were increased (P<0.05). The combination bisoprolol and HCTZ significantly reduced sitting DBP compared to the separate agents as monotherapy (P<0.01). With higher doses of HCTZ, there was a significantly higher incidence of hypokalemia, defined as potassium <3.5 mmol/L (P<0.01). Incidence of hyperuricemia also significantly increased with the increase in HCTZ dose (P<0.01). Adverse events associated with hypokalemia and hyperuricemia were not reported. As the dose of bisoprolol was increased, the frequency and severity of adverse events reported significantly increased (P<0.05). Adverse events reported included asthenia, diarrhea, dyspepsia and somnolence, but severity of effects was not reported. Secondary: Not reported
Frishman et al.[40] (1995) HCTZ 25 mg QD vs bisoprolol 5 mg QD vs bisoprolol and	DB, MC, PC, PG, RCT Patients ≥21 years with mild to moderate (stage II or II) systemic HTN whose body weight was not >10% below or 35% above the ideal weight for height and frame, and were off all	N=547 10 weeks	Primary: Changes in blood pressure and adverse events Secondary: Not reported	Primary: All active treatment groups significantly reduced sitting DBP and SBP from baseline compared to placebo (P<0.01). Addition of HCTZ 6.25 mg contributed significantly to the blood pressure lowering effects of bisoprolol 5 mg. The combination bisoprolol and HCTZ 5-6.25 mg produced a significantly greater reduction in mean sitting DBP from baseline (-12.6±0.5 mm Hg) compared to bisoprolol 5 mg alone (-10.5±0.5 mm Hg; P=0.02) and HCTZ 25 mg alone (-8.5±0.5 mm Hg; P<0.01). Bisoprolol 5 mg monotherapy was significantly better a reducing DBP compared to HCTZ 25 mg alone (P=0.03).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
HCTZ 5-6.25 mg QD (fixed-dose combination product) vs placebo	antihypertensive medications before study entry and sitting DBP was 95 to 115 mm Hg on 3 consecutive weekly visits			The combination bisoprolol and HCTZ 5-6.25 mg produced a significantly greater reduction in mean sitting SBP from baseline (-15.8 mm Hg) compared to bisoprolol 5 mg alone (-10 mm Hg; P<0.01) and HCTZ 25 mg alone (-15.8 mm Hg; P<0.01). There was not a significant difference in mean reduction between bisoprolol 5 mg alone and HCTZ 25 mg alone. Bisoprolol and HCTZ 5-6.25 mg in combination had a 73% response rate compared to 61% for the bisoprolol group and 47% for the HCTZ group. Bisoprolol and HCTZ 5-6.25 mg in combination was found to be significantly more effective compared to bisoprolol 5 mg or HCTZ 25 mg in all subgroups of patients regardless of age, race, gender, or smoking history (P>0.05 for all comparisons). Bisoprolol and HCTZ 5-6.25 mg in combination did not have an increase in frequency or severity of adverse events. The adverse events were comparable to that in the placebo group and frequency among groups was not significant. The most common adverse events reported were headache, dizziness, fatigue, and cough. Significantly greater number patients in the HCTZ 25 mg group (6.5%) experienced hypokalemia (potassium <3.4 mEq/L) compared to the bisoprolol 5 mg group (0.7%; P<0.01), the bisoprolol and HCTZ combination group (0.7%; P<0.01), and placebo (0%; P<0.01). Hyperglycemia occurred in 7.4% of patients in the HCTZ 25 mg group, which was significantly higher than in the placebo group (5.2%; P=0.03). Also, the incidence of hyperuricemia (uric acid >7.5 mg/dL) was significantly higher in the HCTZ 25 mg group (24.4%) compared to placebo (2.7%; P<0.01). Secondary: Not reported
Dafgard et al.[41] (1981)	DB, MC, RCT Patients with	N=31 32 weeks	Primary: Blood pressure, heart rate, adverse	Primary: After the eight week run-in period with HCTZ 25 mg alone, the mean supine blood pressure was significantly reduced from 183/110 to 172/103

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
HCTZ 50 mg QD in the morning vs HCTZ 25 mg QD in the morning vs metoprolol and HCTZ 200-25 mg QD in the morning (fixed-dose combination product)	essential HTN (WHO stages I or II) not adequately controlled (≥160/95 mm Hg) on HCTZ 25 mg/day		events, laboratory values Secondary: Not reported	mm Hg (P<0.01/P<0.01). The increased dose of HCTZ 50 mg following the run-in period did not further significantly reduce the mean blood pressure (165/104 mm Hg). A small but statistically significant reduction in supine heart rate was seen when the HCTZ dose was increased from 25 to 50 mg (82 down to 78 bpm; P<0.05). After the 12 week double-blind period, the mean supine blood pressure was 153/98 mm Hg in the HCTZ 50 mg group. After the 12 week follow-up period, there was not any additional decrease in blood pressure (153/97 mm Hg). Fixed-dose combination product of metoprolol and HCTZ produced a significant reduction in supine blood pressure after 12 weeks of therapy from 172/105 mm Hg on HCTZ 25 mg alone to 154/97 mm Hg on the combination therapy (P<0.001/P<0.01). Similar results were found with the standing blood pressure reductions, from 165/108 to 147/97 mm Hg (P<0.001/P<0.001). After the eight week run-in period, the supine heart rate was 80 bpm which decreased to 64 bpm with the metoprolol and HCTZ fixed-dose combination (P<0.001). The values for standing heart rate demonstrated similar significant reductions (85 to 66 bpm; P<0.001). After the additional 12 week follow-up, the patients in the metoprolol and HCTZ fixed-dose combination group did not demonstrate a significant further reduction in heart rate or blood pressure in any position. Both agents were tolerated and the most common adverse events reported included insomnia, headache, tiredness, and shortness of breath. The majority of events were mild, few were moderate, and none were severe. The only significant changes in laboratory values occurred with the HCTZ 25 and 50 mg groups, where an increase in serum uric acid was observed from 0.30 to 0.34 and 0.35 mmol/L, respectively (P<0.01 and P<0.05; respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Smilde et al.[42] (1983) Metoprolol 400 mg QD in the morning for 5 weeks, followed by metoprolol and HCTZ 200-25 mg QD in the morning (fixed-dose combination product) (group 1) vs metoprolol and HCTZ 200-25 mg QAM for 5 weeks (fixed-dose combination product), followed by metoprolol 400 mg QD in the morning for 5 weeks (group 2)	DB, PG, RCT, XO Patients <65 years with essential HTN (supine DBP ≥95 mm Hg) not controlled on metoprolol 200 mg alone	N=37 15 weeks	Primary: Changes in DBP, SBP, and heart rate Secondary: Not reported	Primary: Both group 1 and 2 significantly reduced DBP (P<0.01) from baseline and the two groups were not significantly different from each other. The combination products significantly reduced SBP from baseline (P<0.05, P<0.01 depending on comparison) Group 2 significantly reduced heart rate at the end of the study compared to baseline (P<0.05). Clinically relevant changes in laboratory parameters or mean body weight were not observed between the groups. Secondary: Not reported
Stevens et al.[43] (1982) <u>Dose-finding phase:</u> propranolol and HCTZ 80-50, 160-50, 240-50, 320-50 mg/day in 2	DB, PG, RCT Patients with mild to moderate essential HTN (DBP 100 to 125 mm Hg)	N=158 25 weeks	Primary: Mean changes of SBP and DB, heart rate, lab values Secondary: Not reported	Primary: After the 12 week dose finding-phase, 94% of patients had a decrease ≥10 mm Hg in DBP. The mean SBP and DBP reduced from 158.0 (±17.3)/105.6 (±6.0) mm Hg to 131.5 (±14.4)/86.4 (± 6.7) mm Hg (P<0.001). After the 10 week portion of the study, there were significantly greater increases (P<0.05) in mean SBP or DBP with propranolol and HCTZ alone vs the combination product of propranolol and HCTZ from the end

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
divided doses (fixed-dose combination product) vs propranolol 80, 160, 240, or 320 mg/day in 2 divided doses <u>Double-blind phase:</u> HCTZ vs propranolol vs propranolol and HCTZ (fixed-dose combination product)				of the dose-finding to the last four biweekly visits to the mean of those visits, and to the last visit. The mean increases of SBP and DBP at the endpoint were: propranolol, 10.2/6.3 mm Hg; HCTZ 13.1/9.3 mm Hg; propranolol-HCTZ combination product 3/1.5 mm Hg. There was a significant decrease in heart rate as the dose of propranolol was increased thought the trial (P>0.30). The only lab value that showed a statistically significant change was serum chloride. The percent of patients that fell outside of the normal range were as follows: propranolol 6/36 (17%), HCTZ 14/37 (38%), and combination 4/28 (14%); P<0.05. Secondary: Not reported
Borhani et al.[44] (1996) MIDAS HCTZ 12.5 to 25 mg QD vs isradipine 2.5 to 5 mg BID	DB, MC, positive-control, RCT Patients, average of 58.5 years old, with HTN	N=883 3 years	Primary: Rate of progression of intimal-medial thickness in carotid arteries Secondary: Rate of cardiovascular events (MI, stroke, CHF, angina,	Primary: There was no difference in the rate of progression of intimal-medial thickness between the treatment groups (P=0.68). Secondary: The rate of cardiovascular events was greater in the isradipine group than in the HCTZ group (5.65 vs 3.17%; P=0.07). The rate of non-major cardiovascular events was greater in the isradipine group than in the HCTZ group (9.05 vs 5.22%; P=0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			sudden death), rate of non-major cardiovascular events and procedures (TIAs, dysrhythmia, aortic valve replacement, femoral popliteal bypass graft), blood pressure	There was a significant decrease in SBP in the HCTZ group as compared to isradipine (-19.5 vs -16.0 mm Hg; P=0.002). There was no difference in change in DBP (both groups, -13.0 mm Hg).
Manyemba et al.[45] (1997) HCTZ 25 mg QD plus reserpine 0.25 mg QD vs HCTZ 25 mg QD plus nifedipine SR 20 mg BID	OL, RCT, XO African American patients aged 21 to 65 years with HTN (blood pressure >140/95 mm Hg) after 4 weeks of daily HCTZ therapy	N=32 10 weeks	Primary: The change in blood pressure from baseline to the end of each 4-week treatment period Secondary: Not reported	Primary: Reserpine reduced SBP by 15.9 mm Hg (95% CI, 8.4 to 23.4) and DBP by 11.1 mm Hg (95% CI, 7.5 to 14.6). Nifedipine SR reduced SBP by 18.9 mm Hg (95% CI, 12.1 to 25.7) and DBP by 9.6 mm Hg (95% CI, 7.2 to 12.0). There was no significant difference between the two groups. Secondary: Not reported
Jamerson et al.[46] (2007) ACCOMPLISH HCTZ 12.5 to 25 mg QD and benazepril 20 to 40 mg QD vs benazepril 20 to 40 mg QD and amlodipine 5 to 10 mg QD	DB, MC, RCT Patients >60 years of age with HTN and at high risk of cardiovascular events	N=10,704 Analysis performed at 6 months (complete trial duration 5 years)	Primary: Changes in mean SBP from baseline to 6 months, blood pressure control rates (SBP/DBP <140/90 mm Hg or <130/89 mm Hg for patients with diabetes and chronic kidney disease) Secondary: Not reported	Primary: At baseline, 97% of subjects were treated with antihypertensive medications at entry, but only 37% of participants had blood pressure control. Mean blood pressure fell from 145/80 to 132/74 mm Hg after six months of treatment with either combination regimen (P<0.001). The six month blood pressure control rate was 73% in the overall trial (78% in the United States), 43% in diabetics, and 40% in patients with renal disease. Of the patients uncontrolled, 61% were not on maximal medications. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Jamerson et al.[47] (2008) ACCOMPLISH HCTZ 12.5 to 25 mg QD and benazepril 20 to 40 mg QD vs benazepril 20 to 40 mg QD and amlodipine 5 to 10 mg QD	AC, DB, MC, RCT Patients >60 years of age with HTN and at high risk of cardiovascular events	N=11,506 36 months (mean)	Primary: The composite of death from cardiovascular causes, nonfatal MI, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and coronary revascularization. Secondary: Death from cardiovascular causes, nonfatal MI, and nonfatal stroke	Primary: There were 552 primary-outcome events in the benazepril plus amlodipine group (9.6%) and 679 events in the benazepril plus HCTZ group (11.8%). The absolute risk reduction with benazepril plus amlodipine therapy was 2.2% and the relative risk reduction was 19.6% compared to benazepril plus HCTZ (HR, 0.80; 95% CI, 0.72 to 0.90; P<0.001). Secondary: For the secondary end point of death from cardiovascular causes, nonfatal MI, and nonfatal stroke, there were 288 (5%) events in the benazepril plus amlodipine group compared to 364 (6.3%) events in the benazepril plus HCTZ group. The absolute risk reduction with benazepril plus amlodipine therapy was 1.3% and the RR reduction was 21.2% compared to benazepril plus HCTZ (HR, 0.79; 95% CI, 0.67 to 0.92; P=0.002).
Bakris et al.[48] (2013) ACCOMPLISH HCTZ 12.5 to 25 mg QD and benazepril 20 to 40 mg QD (B+H) vs benazepril 20 to 40 mg QD and amlodipine 5 to 10 mg QD (B+A)	Post hoc analysis Patients included in the ACCOMPLISH trial (>60 years of age with HTN and at high risk of cardiovascular events) stratified by presence of known CAD at baseline	N=11,506 36 months (mean)	Primary: The composite of death from cardiovascular causes, nonfatal MI, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and coronary revascularization.	Primary: Among the patients with CAD, 13% in the B+A group and 16% in the B+H group reached the primary end point, representing an absolute risk reduction of 3% and a hazard reduction of 18%. The difference in event rates of the composite primary end point between the B+A and B+H groups was significant (HR, 0.80; 95% CI, 0.69 to 0.92; P=0.0016). Among the patients without CAD, fewer patients in the B+A treatment arm (204 of 3,096) reached the primary end point compared with those in the B+H arm (251 of 3,095). The difference in event rates between the B+A and B+H groups was significant (HR, 0.81; 95% CI, 0.67 to 0.98; P=0.026). A comparison of patients with and without CAD event rates for the primary end points demonstrated that the patients with CAD had a greater

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Death from cardiovascular causes, nonfatal MI, and nonfatal stroke	CV event rate than those without CAD (15 vs 7%; P<0.0001). Secondary: The composite secondary end point of CV mortality, MI, and stroke occurred in 5.74% in the B+A group and 8% in the B+H group, resulting in an absolute risk reduction of 1.95% and a hazard reduction of 25% (HR, 0.73; 95% CI, 0.59 to 0.9; P=0.033). The rate of all-cause mortality differed significantly between the treatment arms (HR, 0.77; 95% CI, 0.6 to 0.99; P=0.042). Among the patients without CAD, the rates of CV mortality, MI, and stroke did not differ between the two arms (HR, 0.86; 95% CI, 0.68 to 1.08). The secondary end point events were lower in the group of patients without CAD.
Wing et al.[49] (2003) ANBP2 HCTZ vs enalapril The choice of the specific agent and dose was made by the family practitioner.	MC, OL, PRO, RCT Patients 65 to 84 years of age with average SBP while sitting of ≥160 mm Hg or an average DBP of ≥90 mm Hg (if the SBP was ≥140 mm Hg)	N=6,083 4.1 years (median)	Primary: All cardiovascular events or death from any cause (both initial and subsequent fatal and nonfatal cardiovascular events) Secondary: Not reported	Primary: By the end of the study, blood pressure had decreased to a similar extent in both groups (a decrease of 26/12 mm Hg). There were 695 cardiovascular events or deaths from any cause in the ACE inhibitor group (56.1 per 1,000 patient-years; HR, 0.89; 95% CI, 0.79 to 10; P=0.05) compared to 736 in the diuretic group (59.8 per 1,000 patient-years). The beneficial effects of ACE inhibitor treatment were more evident in male subjects (HR, 0.83; 95% CI, 0.71 to 0.97; P=0.02). The rates of nonfatal cardiovascular events and MI decreased with ACE inhibitor treatment, whereas a similar number of strokes occurred in each group (although there were more fatal strokes in the ACE inhibitor group). Secondary: Not reported
Poldermans et al.[50] (2007) HCTZ 12.5 mg QD and lisinopril 10 to 20 mg	AC, DB, MC, PG, RCT Males and females, ages 18 years and older with HTN (mean DBP ≥110	N=130 6 weeks	Primary: Safety/adverse events, vital signs, hematology, biochemistry variables	Primary: Both treatments were well tolerated, 26 (40.6%) of patients receiving amlodipine and valsartan and 21 (31.8%) of patients receiving lisinopril and HCTZ reported an adverse events and most were not considered drug related. Peripheral edema was reported more often in the amlodipine and valsartan

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs amlodipine 5 to 10 mg QD and valsartan 160 mg QD	mm Hg and <120 mm Hg)		Secondary: Efficacy (mean DBP, response rate, proportion of patients with mean DBP <90 mm Hg or a ≥10 mm Hg reduction from baseline)	group than the lisinopril and HCTZ group (7.7 vs 1.5%) and cough was reported less often in the amlodipine and valsartan group than the receiving lisinopril and hydrochlorothiazide group (1.6 vs 3.0%). No difference was found between the treatments in changes in laboratory values or biochemistry variables. Secondary: Both treatments led to a reduction in mean SBP and DBP (P<0.0001 for both from baseline) but were not significantly different from each other. Mean blood pressure for each group at study end: amlodipine and valsartan 135.0/83.6 mm Hg and lisinopril and HCTZ 138.7/85.2 mm Hg. The response rate was similar among the groups (100 vs 95.5%; P value not significant).
Fogari et al.[51] (2007) CANDIA HCTZ 12.5 mg QD and candesartan 16 mg vs amlodipine 10 mg QD	DB, MC, RCT Patients, 20 to 80 years old, with mild to moderate uncomplicated HTN not controlled on monotherapy with an antihypertensive (SBP <180 mg Hg and DBP 90 to 110 mg Hg)	N=203 8 weeks	Primary: Decrease in DBP Secondary: Sitting SBP, reduction of the orthostatic blood pressure at least two minutes after standing, change in heart rate, percentage of patients normalized (DBP <90 mm Hg and SBP <140 mm Hg), percentage of responders (reduction in DBP ≥5 mm Hg)	Primary: There was no significant difference in the mean decrease in DBP between treatment groups; the difference in final DBP was -0.02 mm Hg (95% CI, -1.48 to 1.52 mm Hg; P=0.979). Secondary: There was no significant difference between the groups at week eight for the following: sitting SBP (P=0.835), heart rate (P<0.500), orthostatic SBP (P=0.883), orthostatic DBP (P=0.264), percentage of patients normalized (P=10), percentage of responders (P=0.900). The number of patients reporting an adverse event was greater in the amlodipine group (P=0.001). The number of patients reporting an adverse drug-related event was greater in the amlodipine group (P<0.001). Changes in blood chemistry and other secondary measurements were not significantly different between the treatment groups.
Neutel et al.[52] (2008)	AC, DB, RCT	N=538	Primary: Change in SBP	Primary: At week eight, there was a reduction in SBP of 27.1 mm Hg with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
HCTZ 25 mg QD and irbesartan 300 mg vs irbesartan 300 mg QD vs HCTZ 25 mg QD	Patients with moderate HTN (seated SBP 160 to 179 mm Hg when DBP <110 mm Hg; or DBP 100 to 109 mm Hg when SBP <180 mm Hg)	12 weeks	after week 8 Secondary: Change from baseline in DBP at weeks 8 and 12, SBP at week 12, proportion of responders (SBP <140 mm Hg and DBP <90 m Hg) at weeks 8 and 12	irbesartan and HCTZ compared to 22.1 mm Hg with irbesartan monotherapy (P=0.0016) and 15.7 mm Hg with HCTZ (P<0.0001). Secondary: At week eight, there was a reduction in DBP of 14.6 mm Hg with irbesartan and HCTZ compared to 11.6 mm Hg with irbesartan monotherapy (P=0.0013) and 7.3 mm Hg with HCTZ (P<0.0001). A significantly greater percentage of patients reached a treatment goal of SBP <140 mm Hg and DBP <90 mm Hg by week eight with irbesartan and HCTZ (53.4%) compared with irbesartan (40.6%; P=0.0254) and HCTZ (20.2%; P<0.0001) alone. Treatment was well tolerated in all three treatment groups with a slight increase in adverse events in the combination therapy group.
Salerno et al.[53] (2004) HCTZ 12.5 mg QD and losartan 50 mg vs losartan 50 to 100 mg QD Doses were titrated as needed to reach blood pressure goal (<90 mm Hg).	DB, RCT Patients with severe HTN	N=585 6 weeks	Primary: Proportion of patients achieving goal blood pressure Secondary: Adverse events	Primary: Almost twice as many patients achieved goal blood pressure at four weeks on losartan 50 mg and HCTZ 12.5 mg vs losartan 50 to 100 mg monotherapy (P=0.002). Almost three times as many patients achieved goal blood pressure at six weeks with losartan and HCTZ vs losartan monotherapy (P<0.001). Adverse experiences on losartan and HCTZ (43%) were significantly less than with losartan monotherapy (53%).
Minami et al.[54] (2007) HCTZ 12.5 mg/day and losartan 50 mg/day	OL Japanese outpatients with essential HTN treated for ≥2 months with either	N=15 12 months	Primary: Changes in blood pressure Secondary: Not reported	Primary: In patients who had previously received candesartan, 24-hour blood pressure decreased significantly from 137/89 mm Hg to 126/81 mm Hg after three months (P<0.05/P<0.001) and to 123/81 mm Hg after 12 months (P<0.01/P<0.001) of treatment with losartan and HCTZ.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs candesartan 8 mg QD or amlodipine 5 mg QD	candesartan or amlodipine and 24-hour ambulatory blood pressure ≥135/80 mm Hg			In patients who had previously received amlodipine, 24-hour blood pressure decreased significantly from 137/81 to 125/75 mm Hg after three months (P<0.05/P<0.05) and to 124/77 mm Hg after 12 months (P<0.05/P value not significant) of treatment with losartan and HCTZ. There were significant decreases in SBP during the daytime, nighttime and early morning after 12 months in both groups. No adverse changes in the indices of glucose or lipid metabolism were observed in either group. Secondary: Not reported
Chrysant et al.[55] (2004) HCTZ 12.5 to 25 mg QD and olmesartan 10 to 40 mg QD vs olmesartan 10 to 40 mg QD vs HCTZ 12.5 to 25 mg QD vs placebo	DB, RCT, factorial design Patients with a baseline mean seated DBP of 110 to 115 mm Hg	N=502 8 weeks	Primary: Change in DBP at week 8 Secondary: Change in SBP at week 8	Primary: Olmesartan and HCTZ produced greater reductions in seated DBP at week eight than did monotherapy with either component. All olmesartan and HCTZ combinations significantly reduced DBP compared with placebo in a dose-dependent manner. Reductions in mean trough DBP were 8.2, 16.4, and 21.9 mm Hg with placebo, olmesartan 20 mg plus HCTZ 12.5 mg, and olmesartan 40 mg plus HCTZ 25 mg, respectively. Secondary: Olmesartan and HCTZ produced greater reductions in seated SBP at week eight than did monotherapy with either component. All olmesartan and HCTZ combinations significantly reduced DBP compared with placebo in a dose-dependent manner. Reductions in mean trough SBP were 3.3, 20.1, and 26.8 mm Hg with placebo, olmesartan 20 mg plus HCTZ 12.5 mg, and olmesartan 40 mg plus HCTZ 25 mg, respectively. All treatments were well tolerated.
White et al.[56] (2008) Val-DICTATE	DB, MB, RCT Patients with stage 1	4 weeks Duration not	Primary: Percentage of patients whose	Primary: A significantly higher proportion of hypertensive patients met blood pressure control levels in the valsartan and HCTZ group (37%) compared

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
HCTZ 25 mg QD vs valsartan and HCTZ 160-12.5 mg QD (fixed-dose combination product)	to 2 HTN whose BP remained uncontrolled on HCTZ 12.5 mg	reported	clinic blood pressure values were <140/90 mm Hg and blood pressure values Secondary: Not reported	with the HCTZ group (16%; P<0.001). Changes in SBP and DBP were significantly greater with valsartan and HCTZ (-12. 4/-7.5 mm Hg) compared to HCTZ (-5.6/-2.1 mm Hg; P<0.001). Secondary: Not reported
White et al.[57] (2008) HCTZ 25 mg QD and valsartan 160 mg vs HCTZ 25 mg QD and telmisartan 80 mg vs placebo	DB, PC, RCT Hypertensive patients	N=1,181 8 weeks	Primary: Changes in DBP and SBP at 8 weeks Secondary: Safety	Primary: Changes from baseline in blood pressure following telmisartan and HCTZ (-24.6/-18.2 mm Hg) were significantly greater than both valsartan and HCTZ (-22.5/-17.0 mm Hg; P=0.017 for SBP and P=0.025 for DBP), and placebo (-4.1/-6.1 mm Hg; P<0.0001). Secondary: The total number of patients with at least one adverse event reported was similar among the three treatment groups and was 37% for valsartan and HCTZ, 36% for telmisartan and HCTZ, and 42% for placebo.
Waeber et al.[58] (2001) Valsartan 80 mg QD, which was switched to valsartan 80 mg and HCTZ 12.5 mg QD or valsartan 80 mg and benazepril 10	OL, RCT Patients with mild-to-moderate uncontrolled HTN (DBP ≥90) while on valsartan monotherapy	N=327 4 weeks	Primary: Efficacy and safety Secondary: Not reported	Primary: The two combinations produced an additional blood pressure reduction compared to monotherapy (P<0.001 for both), with similar DBP reductions reported for the two combination groups (-4.5 mm Hg with valsartan plus HCTZ and -3.3 mm Hg with valsartan plus benazepril). SBP reductions of -6.7 and -3.2 mm Hg with valsartan plus HCTZ and valsartan plus benazepril, respectively, were reported (P=0.1). At the end of the trial, the blood pressure of the responders to valsartan monotherapy was lower than that of patients requiring combination

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg QD				therapy. Valsartan given alone or in association with HCTZ or benazepril was well tolerated. Secondary: Not reported
Izzo Jr et al.[59] (2011) ValVET Valsartan and HCTZ 160-12.5 mg QD (fixed-does combination product) vs valsartan 160 mg QD vs HCTZ 12.5 mg QD All patients were allowed to up titrate study medication if blood pressure did not improve.	DB, RCT Patients ≥70 years of age with systolic HTN	N=384 16 weeks	Primary: Change in baseline SBP at week 4 Secondary: Time to blood pressure control	Primary: At week four, reductions in baseline SBP were significantly greater with combination therapy (-17.3 mm Hg) compared to valsartan (-8.6 mm Hg; P<0.001). At this time, reductions with combination therapy and HCTZ were similar (-17.3 vs -13.6 mm Hg; P=0.096). Secondary: Median time to blood pressure control was significantly shorter with combination therapy compared to HCTZ (four vs eight weeks; P<0.05) and valsartan (four vs 12 weeks; P<0.0001).
Duprez et al.[60] (abstract) (2011) ValVET	Subgroup analysis Patients ≥70 years of age with systolic	N=108 Duration not specified	Primary: Change in ambulatory SBP	Primary: Initiation of treatment with combination valsartan and HCTZ reduced ambulatory blood pressure more effectively compared to monotherapy with either valsartan or HCTZ throughout daytime, night-time, and 24 hr

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Valsartan and HCTZ 160-12.5 mg QD (fixed-does combination product) vs valsartan 160 mg QD vs HCTZ 12.5 mg QD All patients were allowed to up titrate study medication if blood pressure did not improve.	HTN		Secondary: Safety	monitoring periods, as well as during the last four to six hour dosing periods. Twenty-four hour ambulatory blood pressure was reduced from 141.1/76.5 to 125.8/69.2 mm Hg by week four with combination valsartan and HCTZ compared to reductions from 142.2/78.7 to 139.1/77.5 mm Hg with HCTZ and 142.2/78.3 to 136.4/75.1 mm Hg with valsartan (P<0.01 for all). Secondary: In the overall study, tolerability was similar among the three treatment groups.
Schmieder et al.[61] (2009) HCTZ 12.5 to 25 mg QD (with optional addition of amlodipine 5 to 10 mg QD) vs aliskiren 150 to 300 mg QD (with optional addition	AC, DB, RCT Adults with essential HTN	N=1,124 12 months	Primary: Safety and change in mean sitting DBP Secondary: Change in mean sitting SBP	Primary: The proportion of patients who experienced adverse events during the six week placebo-controlled period was similar in the aliskiren monotherapy, HCTZ monotherapy, and placebo groups (26.4, 24.5, and 28.5%, respectively). During the 52 week double-blind treatment period, adverse events were reported by a similar proportion of patients receiving the aliskiren and hydrochlorothiazide regimens. Most adverse events were mild or moderate in intensity. At week 26, the aliskiren regimen provided significantly greater reductions from baseline in DBP compared to HCTZ (-14.2 and -13.0 mm Hg, respectively; P<0.05). The greater reduction in DBP with the aliskiren

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
of amlodipine 5 to 10 mg QD) vs placebo for 6 weeks, then randomized to either aliskiren 300 mg QD or HCTZ 25 mg QD				regimen compared with the HCTZ regimen was maintained at week 52 (-16.0 and -15.0 mm Hg, respectively; P<0.05). Secondary: At week 26, the aliskiren regimen provided significantly greater reductions from baseline in SBP compared to HCTZ (-20.3 and -18.6 mm Hg, respectively; P<0.05). Reductions in SBP at week 52 were not inferior to those of HCTZ (-22.1 and -21.2 mm Hg, respectively; P<0.0001 for non-inferiority).
Schmieder et al.[62] (2009) HCTZ 12.5 mg QD, followed by 25 mg QD after 3 weeks vs aliskiren 150 mg QD, followed by 300 mg QD after 3 weeks vs placebo, followed by aliskiren 300 mg QD or HCTZ 25 mg QD after 6 weeks	Subgroup analysis of obese patients in Schmieder et al. Patients 18 years of age and older with essential HTN, a mean sitting DBP ≥90 and <110 mm Hg; at randomization, patients had to have a mean sitting DBP ≥95 and <110 mm Hg and show a difference of ≤10 mm Hg since the previous visit	N=1,124 52 weeks	Primary: Mean sitting DBP Secondary: Mean sitting SBP at week 26, mean sitting DBP and SBP at week 52, proportion of patients with response to treatment, blood pressure control at weeks 26 and 52, and safety	Primary: The least squares mean DBP and SBP reductions at week 12 were significantly greater with aliskiren compared to HCTZ (P<0.0001 and P=0.001 respectively). Secondary: At week 52, aliskiren resulted in significantly greater mean sitting DBP reductions compared to HCTZ (P<0.001). Blood pressure response rates were significantly greater with aliskiren compared to HCTZ at both week 12 and week 52 (P<0.05). Significantly more obese patients achieved blood pressure control with aliskiren compared to HCTZ at week 12 (P=0.0013). Blood pressure control rates were similar between groups at week 52 (P value not reported).
Villamil et al.[63] (2007) HCTZ 6.25 to 25	DB, MC, PC, RCT Men and women ≥18 years with	N=2,776 8 weeks	Primary: Change in mean sitting DBP	Primary: Aliskiren monotherapy significantly reduced mean sitting DBP (P=0.0002). Only the aliskiren 150 and 300 mg doses were more effective than placebo (P=0.09 for aliskiren 75 mg). HCTZ monotherapy

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg QD vs aliskiren 75 to 300 mg QD vs aliskiren and HCTZ (every dose combination except aliskiren 300 mg and HCTZ 6.25 mg) QD vs placebo	mild-to-moderate essential HTN		Secondary: Change in mean sitting SBP, dose-response efficacy for all treatment groups, proportion achieving a successful response (DBP <90 mm Hg or ≥10 mm Hg), proportion achieving blood pressure control (<140/90 mm Hg), plasma renin activity, renin concentrations, safety	significantly reduced DBP from baseline (P<0.01 for all vs placebo). All combinations were more effective than placebo (P<0.0001) with reductions in DBP ranging from 10.4 to 14.3 mm Hg. Most combination regimens were more effective than monotherapy with the individual components (exceptions were aliskiren 150 mg and HCTZ 6.25 mg vs monotherapy, and aliskiren 75 mg and HCTZ 12.5 mg vs HCTZ monotherapy). Secondary: After eight weeks of therapy, aliskiren 150 and 300 mg regimens (both P<0.0001) were more effective than placebo in lowering mean sitting SBP, but the 75 mg dose was not (P=0.151). Combination therapy was consistently more effective in reducing SBP than monotherapy with the individual components, with the exception of aliskiren 75 mg plus HCTZ 12.5 vs HCTZ monotherapy. Reductions in SBP with combination therapy ranged from 14.3 to 21.2 mm Hg. Blood pressure reductions were related to the doses of both aliskiren and HCTZ. Responder rates were significantly higher with aliskiren 300 mg (63.9%; P=0.0005), HCTZ 12.5 and 25 mg (60.6 and 59.0%, respectively; both P<0.02) and all combination doses (58.4 to 80.6%; all P<0.05) than placebo (45.8%). Responder rates for all combinations of aliskiren and HCTZ 25 mg, and aliskiren 300 mg and HCTZ 12.5 mg were higher than both monotherapies (P<0.05), while aliskiren 75 mg and HCTZ 12.5 mg and aliskiren 150 mg and HCTZ 12.5 mg were more effective than their respective aliskiren monotherapies (P<0.05). In the aliskiren and HCTZ monotherapy groups, only aliskiren 300 mg led to statistically significantly greater control rates than placebo (46.7 vs 28.1%; P=0.0001). Control rates for all combinations, with the exception of aliskiren 75 mg and HCTZ 6.25 mg, were higher than placebo (all P<0.02). There was a trend towards improved control rates with combination therapy (37.4 to 59.5%) compared to aliskiren monotherapy

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(29.0 to 46.7%) or HCTZ monotherapy (32.5 to 37.8%). Combinations utilizing the higher doses of one or both drugs (aliskiren 75 to 300 mg with HCTZ 25 mg or aliskiren 150 to 300 mg with HCTZ 12.5 mg) yielded control rates that were significantly higher than monotherapy with either component. While all doses of aliskiren decreased plasma renin activity and all doses of HCTZ increased plasma renin activity, combination therapy resulted in decreased plasma renin activity of 46.1 to 63.5%. Renin concentrations increased in all monotherapy and combination regimens with the exception of HCTZ 6.25 and 12.5 mg. All active treatments were well tolerated with 37.3 to 39.2% of patients experiencing adverse events with aliskiren monotherapy, 38.7 to 42.0% with HCTZ monotherapy, 34.6 to 45.3% with aliskiren and HCTZ, and 44% with placebo. Hypokalemia (serum potassium <3.5 mmol/L) occurred with the highest frequency with HCTZ 12.5 and 25 mg (3.9 and 5.2%, respectively). When administered in combination with aliskiren, the frequency of hypokalemia was 0.7 to 2.0% with HCTZ 12.5 mg and 2.2% to 3.4% with HCTZ 25 mg.
Blumenstein et al.[64] (2009) HCTZ 25 mg (existing therapy) vs aliskiren and HCTZ 300-25 mg QD (fixed-dose combination product) vs	DB, MC, RCT Patients with HTN and an inadequate response to HCTZ (mean sitting DBP >90 and ≤110 mm Hg following 4 weeks of HCTZ 25 mg)	N=722 8 weeks	Primary: Changes in mean sitting SBP/DBP, proportion of patients achieving blood pressure control (mean sitting blood pressure <140/90 mm Hg), and blood pressure response rates (msDBP <90 mm Hg or a ≥10 mm Hg decrease from baseline)	Primary: The mean reductions in mean sitting SBP/DBP from baseline with aliskiren and HCTZ 300-25 and 150-25 mg were significantly greater compared to those achieved with HCTZ monotherapy (P<0.001 for all). Rates of blood pressure control were significantly higher with aliskiren and HCTZ 300-25 and 150-25 mg compared to HCTZ monotherapy (P<0.001 for both). Aliskiren and HCTZ 300-25 mg provided significantly greater reductions in mean sitting SBP/DBP and rates of blood pressure control compared to aliskiren and HCTZ 150-25 mg dose (P<0.05 for all). Blood pressure response rates were significantly higher with aliskiren and HCTZ 300-25mg (78.5%) and aliskiren and HCTZ 150-25 mg (67.4%) compared to HCTZ monotherapy (47.1%; P<0.001 for both comparisons).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
aliskiren and HCTZ 150-25 mg QD (fixed-dose combination product)			Secondary: Not reported	All treatments were generally well-tolerated and the proportion of patients experiencing adverse events was similar across treatment groups. The majority of adverse events were mild and transient. Adverse events reported in >2% of patients were nasopharyngitis, dizziness, back pain, and vertigo. The proportion of patients with serum potassium <3.5 mmol/L was lower with aliskiren and HCTZ (1.3 to 2.2%) compared to HCTZ monotherapy (3.4%). Hyperkalemia (serum potassium >5.5 mmol/L) was observed in only one patient receiving aliskiren and HCTZ and two patients in the HCTZ monotherapy group. No patient had increases in serum creatinine above the pre-specified clinically significant threshold. Secondary: Not reported
Jordan et al.[65] (2007) HCTZ 25 mg QD (existing therapy) vs aliskiren 150 to 300 mg QD, added to existing HCTZ therapy (single entity products) vs amlodipine 5 to 10 mg QD, added to existing HCTZ therapy (single entity products)	DB, DD, MC, PG, RCT Obese men and women (BMI ≥30 kg/m^2) ≥18 years with essential HTN (mean sitting DBP 95 to 109 mm Hg and SBP <180 mm Hg) who had not responded to 4 weeks of treatment with HCTZ 25 mg	N=489 12 weeks	Primary: Change in mean sitting DBP with aliskiren 300 mg plus HCTZ vs HCTZ alone at 8 weeks Secondary: Comparisons of mean sitting DBP and SBP with aliskiren plus HCTZ vs the other treatment groups, percentage of responders (mean sitting DBP <90 mm Hg or ≥10 mm Hg reduction from baseline), proportion of	Primary: Aliskiren 300 mg added to HCTZ 25 mg significantly reduced mean sitting DBP compared with HCTZ alone at week eight (mean difference, -4.0; P<0.0001). Secondary: Aliskiren 300 mg added to HCTZ caused numerically larger reductions in mean sitting DBP and SBP compared with amlodipine 10 mg plus HCTZ and irbesartan 300 mg plus HCTZ at week eight, but there were no statistically significant differences between treatment groups (P>0.05). Responder rates were significantly higher with aliskiren plus HCTZ than HCTZ alone at week eight (P=0.0193) and week 12 (P=0.004) but comparable to responder rates observed with amlodipine plus HCTZ (P>0.05) and irbesartan plus HCTZ (P>0.05). The proportion of patients achieving blood pressure control was significantly higher with aliskiren plus HCTZ than HCTZ alone at week eight (P=0.0005) and week 12 (P=0.0001) but not statistically different than amlodipine plus HCTZ (P>0.05) and irbesartan plus HCTZ (P>0.05). Plasma renin activity significantly increased (P<0.05) during four weeks

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs irbesartan 150 to 300 mg QD, added to existing HCTZ therapy (single entity products)			patients achieving blood pressure control (mean sitting blood pressure <140/90 mm Hg), plasma renin activity, safety and tolerability	of HCTZ monotherapy. Combination with aliskiren neutralized this increase and led to an overall significant reduction in plasma renin activity compared with pretreatment baseline (P<0.05) whereas amlodipine and irbesartan led to further significant increases (P<0.05). All of the study treatments were generally well tolerated. Amlodipine plus HCTZ (45.2%) was associated with a higher incidence of adverse events than the other treatment groups (36.1 to 39.3%), largely due to a higher rate of peripheral edema (11.1 vs 0.8 to 1.6%).
Geiger et al.[66] (2009) HCTZ 25 mg QD vs aliskiren 150 to 300 mg QD, added to existing HCTZ therapy vs valsartan 160 to 320 mg QD, added to existing HCTZ therapy vs aliskiren 150 to 300 mg and valsartan 160 to 320 mg QD, added to existing HCTZ therapy	AC, DB, RCT Patients ≥18 years of age with mild to moderate essential HTN who were taking HCTZ for 4 weeks with a DBP ≥95 mm Hg	N=641 8 weeks	Primary: Change in DBP at week 8 Secondary: Change SBP at week 8, change in DBP and SBP at week 4, proportion of patients achieving blood pressure control (SBP/DBP <140/90 mm Hg), change in plasma renin activity, plasma renin concentration	Primary: After eight weeks of therapy, the triple therapy showed significantly greater reductions in SBP and DBP compared with the other groups. The additional SBP and DBP reductions were 7 and 5 mm Hg, respectively compared to aliskiren and HCTZ (P<0.0001), 3 and 2 mm Hg compared to valsartan and HCTZ (P<0.01), and 15 and 10 mm Hg compared to HCTZ monotherapy (P<0.001). Aliskiren and HCTZ and valsartan and HCTZ combination therapies were more effective compared to HCTZ monotherapy. Valsartan and HCTZ was more effective than aliskiren and HCTZ. SBP and DBP were reduced by 15 and 11 mm Hg, respectively in the aliskiren and HCTZ group. SBP and DBP were reduced by 18 and 14 mm Hg, respectively, in the valsartan and HCTZ group. Secondary: Blood pressure control rate was significantly higher with triple therapy compared to aliskiren and HCTZ (40.9%, P<0.001), valsartan and HCTZ (48.7%, P<0.001), and HCTZ monotherapy (20.5%, P<0.001). At week four, a significantly greater blood pressure control rate was observed for the triple therapy group at lower doses (150-160-25 mg) compared to the respective doses of the other groups: aliskiren and valsartan and HCTZ (300-320-25 mg) group (56%) compared to aliskiren and HCTZ (36.6%, P<0.05), valsartan and HCTZ (42.2%, P<0.05), and HCTZ monotherapy (19.9%, P<0.01). At week eight, plasma renin concentration was unchanged in the HCTZ

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				group, but was significantly increased in other groups. A significant decrease in plasma renin activity from baseline was observed in the aliskiren and HCTZ group (P<0.001) and a significant increase was observed in the valsartan and HCTZ (P<0.001). In the HCTZ and triple therapy groups, there was no change in plasma renin activity (both P>0.75).
O'Brien et al.[67] (2007) Aliskiren 150 mg QD for 3 weeks, then HCTZ 25 mg QD was added for an additional 3 weeks (if ABPM remained ≥135/85 mm Hg) vs irbesartan 150 mg QD for 3 weeks, then aliskiren 75 mg QD added for 3 weeks, then aliskiren 150 mg QD added for 3 weeks vs ramipril 5 mg QD for 3 weeks, then aliskiren 75 mg QD added for 3 weeks, then aliskiren 150 mg	3 OL studies Men and women 18 to 80 years with ambulatory SBP ≥140 and ≤180 mm Hg without treatment	N=67 6 to 9 weeks	Primary: Change in daytime systolic ABPM with combination therapy compared with monotherapy Secondary: Change in daytime diastolic ABPM, nighttime systolic and diastolic ABPM, daytime and nighttime heart rates, plasma renin activity	Primary: Aliskiren coadministered with HCTZ (P=0.0007) or ramipril (P=0.03) led to significantly greater reductions in daytime systolic ABPM compared to monotherapy. There was a trend for a reduction in daytime systolic ABPM with the addition of aliskiren to irbesartan; however, this trend was not statistically significant. Secondary: Aliskiren plus HCTZ significantly lowered daytime diastolic ABPM compared to aliskiren monotherapy (P=0.0006). Changes in nighttime systolic and diastolic ABPM followed similar trends but did not achieve statistical significance (P=0.06 and P=0.09, respectively). No changes in heart rate were observed with either aliskiren regimen. Aliskiren added to irbesartan did not significantly change diastolic ABPM compared to irbesartan monotherapy; however, nighttime systolic and diastolic ABPM were significantly reduced (P<0.05 for all). No changes in heart rate were observed with either irbesartan regimen. Mean diastolic ABPM was significantly decreased with the addition of aliskiren 150 mg (P<0.05) but not aliskiren 75 mg to ramipril monotherapy. Both aliskiren doses significantly decreased nighttime systolic and diastolic ABPM (P<0.05 for all). No changes in heart rate were observed with either ramipril regimen. Aliskiren alone significantly inhibited plasma renin activity by 65% (P<0.0001), while ramipril and irbesartan monotherapy increased renin activity by 90 and 175%, respectively. When aliskiren was coadministered with HCTZ, ramipril or irbesartan, plasma renin activity remained similar to baseline levels or decreased.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD added for 3 weeks				
Pepine et al.[68] (2003) INVEST Verapamil SR 240 mg/day (step 1), then add trandolapril if needed (step 2), then increase doses of both (step 3), then add HCTZ (step 4) (calcium antagonist strategy) vs atenolol 50 mg/day (step 1), then add HCTZ if needed (step 2), then increase doses of both (step 3), then add trandolapril (step 4) (non-calcium antagonist strategy) Trandolapril was recommended for all patients with heart failure, diabetes, or renal insufficiency.	MC, OL, RCT Patients with essential HTN	N=22,576 24 months	Primary: First occurrence of death (all cause), nonfatal MI or stroke Secondary: Cardiovascular death, angina, cardiovascular hospitalization, angina, blood pressure control (SBP/DBP <140/90 mm Hg or <130/85 mm Hg if diabetic or renal impairment), safety	Primary: At 24 months, in the calcium antagonist strategy subgroup, 81.5% of patients were taking verapamil SR, 62.9% trandolapril, and 43.7% HCTZ. In the non-calcium antagonist strategy, 77.5% of patients were taking atenolol, 60.3% HCTZ, and 52.4% trandolapril. After a follow-up of 61,835 patient-years (mean, 2.7 years per patient), 2,269 patients had a primary outcome event with no statistically significant difference between treatment strategies (9.93% in calcium antagonist strategy vs 10.17% in non-calcium antagonist strategy; RR, 0.98; 95% CI, 0.90 to 16; P=0.57). Secondary: There was no significant difference in the rate of cardiovascular death (P=0.94) or cardiovascular hospitalization (P=0.59) between the two treatment groups. At 24 months, angina episodes decreased in both groups, but the mean frequency was lower in the calcium antagonist strategy group (0.77 episodes/week) compared to the non-calcium antagonist strategy group (0.88 episodes/week; P=0.02). Two-year blood pressure control was similar between groups. The blood pressure goals were achieved by 65.0% (systolic) and 88.5% (diastolic) of calcium antagonist strategy patients and 64.0% (systolic) and 88.1% (diastolic) of non-calcium antagonist strategy patients. A total of 71.7% of calcium antagonist strategy patients and 70.7% of non-calcium antagonist strategy patients achieved an SBP <140 mm Hg and DBP <90 mm Hg. Both regimens were generally well tolerated. Patients in the calcium antagonist strategy group reported constipation and cough more frequently than patients in the non-calcium antagonist strategy group, while non-calcium antagonist strategy patients experienced more dyspnea, lightheadedness, symptomatic bradycardia and wheezing (all were statistically significant with P≤0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Hansson et al.[69] (1999) STOP-Hypertension Atenolol 50 mg or metoprolol 100 mg or pindolol 5 mg QD and/or HCTZ 25 mg with amiloride 2 to 5 mg QD vs enalapril 10 mg or lisinopril 10 mg QD vs felodipine 2.5 mg or isradipine 2.5 mg QD	MC, OL, PRO, RCT Men and women, age 70to 84 years with HTN (SBP ≥180mm Hg or DBP ≥105 mm Hg or both)	N=6,614 4 years	Primary: Fatal stroke, fatal MI, other fatal cardiovascular events Secondary: Blood pressure	Primary: The rate of prevention of cardiovascular deaths was similar in all groups (RR, 0.97 to 14; 95% CI, 0.86 to 1.26). Fatal cardiovascular events, including fatal stroke and fatal myocardial infarction MI, occurred in 19.8 per 1,000 patient-years in the β-blocker and/or HCTZ group, in the felodipine or isradipine group and in the enalapril or lisinopril group (RR, 0.99; 95% CI, 0.84 to 1.16). The RR of cardiovascular death in patients in the enalapril or lisinopril group as compared to the felodipine or isradipine group was 14 (95% CI, 0.86 to 1.26; P=0.67.) Secondary: Decreases in blood pressure were similar among the groups.
Pepine et al.[70] (2006) INVEST Verapamil SR (step 1), then add trandolapril if needed (step 2), then increase doses of both (step 3), then add HCTZ (step 4) (calcium antagonist	Post hoc analysis of INVEST Patients with essential HTN	N=22,576 24 months	Primary: Risk for adverse outcome associated with baseline factors, follow-up blood pressure and drug treatments Secondary: Not reported	Primary: Previous heart failure (adjusted HR, 1.96), as well as diabetes (HR, 1.77), increased age (HR, 1.63), United States residency (HR, 1.61), renal impairment (HR, 1.50), stroke/TIA (HR, 1.43), smoking (HR, 1.41), MI (HR, 1.34), PVD (HR, 1.27), and revascularization (HR, 1.15) predicted increased risk. Follow-up SBP <140 mm Hg (HR, 0.82) or DBP <90 mm Hg (HR, 0.70) and trandolapril with verapamil SR (HR, 0.78 and 0.79) were associated with reduced risk. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
strategy) vs atenolol (step 1), then add HCTZ if needed (step 2), then increase doses of both (step 3), then add trandolapril (step 4) (non-calcium antagonist strategy)				
Conlin et al.[71] (2000) PREVAIL Low-dose HCTZ plus ARB vs candesartan 8 to 16 mg QD, irbesartan 150 to 300 mg QD, losartan 50 to 100 mg QD, and valsartan 80 to 160 mg QD vs another ARB	MA Patients with HTN	N=11,281 (43 trials) Duration varied	Primary: Weighted average for SBP and DBP reduction with ARB monotherapy, dose titration, and with the addition of low-dose HCTZ were calculated; responder rates Secondary: Not reported	Primary: The absolute weighted-average reductions in DBP (8.2 to 8.9 mm Hg) and SBP (10.4 to 11.8 mm Hg) for ARB monotherapy were comparable for all ARBs. Responder rates for ARB monotherapy were 48 to 55%. Dose titration resulted in slightly greater blood pressure reductions and an increase in responder rates of 53 to 63%. ARB and HCTZ combinations produced substantially greater reductions in SBP (16.1 to 20.6 mm Hg) and DBP (9.9 to 13.6 mm Hg) than ARB monotherapy. Responder rates for ARB and HCTZ combinations were 56 to 70%. The authors concluded that candesartan, irbesartan, losartan, and valsartan produced comparable antihypertensive efficacy when administered at their recommended doses, a near flat dose response when titrating from starting to maximum recommended dose, and substantial potentiation of the antihypertensive effect with addition of HCTZ. Secondary: Not reported
Stanton et al.[72] (2010)	MA	N=4,877 (8 trials)	Primary: Paradoxical blood	Primary: There were no significant differences among the pooled aliskiren,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Irbesartan, losartan, valsartan, ramipril, HCTZ, placebo vs aliskiren 300 mg QD	Adults with mild to moderate essential HTN	4 to 12 weeks	pressure rises, as well as the percentage of patients with SBP increases (>10 or >20 mm Hg) or DBP increases (>5 or >10 mm Hg) from baseline Secondary: Not reported	irbesartan, losartan, valsartan, ramipril, and HCTZ groups in the incidence of SBP increases >10 mm Hg (P=0.30) and >20 mm Hg (P=0.28) or DBP increases >5 mm Hg (P=0.65) and >10 mm Hg (P=0.5). Increases in SBP and DBP occurred significantly more frequently in the pooled placebo group than the aliskiren group (P<0.001). Secondary: Not reported
Hannson et al.[73] (2000) NORDIL Conventional therapy (diuretic, β-blocker or both) vs diltiazem 180 to 360 mg QD	BE, MC, OL, PRO, RCT Patients 50 to 74 years of age with DBP ≥100 mm Hg and previously untreated	N=10,881 4.5 years	Primary: Combined fatal and nonfatal stroke, fatal and nonfatal MI, other cardiovascular death Secondary: Fatal plus nonfatal stroke and fatal plus nonfatal MI	Primary: The primary endpoint occurred in 403 of the diltiazem patients and 400 of the diuretic/β-blocker patients (RR, 1.00; 95% CI, 0.87 to 1.15; P=0.97). Secondary: Rates of secondary endpoints were similar between the groups. Fatal plus nonfatal stroke occurred in 159 of the diltiazem patients and 196 of the diuretic/β-blocker patients (P=0.04). Fatal plus nonfatal MI occurred in 183 of the diltiazem patients and 157 of the diuretic/β-blocker patients (P=0.17). Other endpoints were not statistically different between the groups including cardiovascular death (P=0.41), all cardiac events (P=0.57 and congestive heart failure (P=0.42).
Messerli et al.[74] (1998) Diuretics (amiloride, chlorthalidone, HCTZ, HCTZ and triamterene [fixed-dose combination product], or	MA 10 RCTs lasting ≥1 year, which used as first line agents diuretics and/or β-blockers and reported morbidity and mortality	N=16,164 1 year	Primary: Cardiovascular morbidity and mortality, all-cause morbidity Secondary: Not reported	Primary: Diuretic treatment significantly reduced the odds for cardiovascular mortality by 25% (OR, 0.75; 95% CI, 0.64 to 0.87), while β-blockers did not reduce cardiovascular mortality (OR, 0.98; 95% CI, 0.78 to 1.23; P values not reported). Diuretic treatment significantly reduced the odds for all-cause mortality by 14% (OR, 0.86; 95% CI, 0.77 to 0.96), while β-blockers did not reduce all-cause mortality (OR, 1.05; 95% CI, 0.88 to 1.25; P values not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
thiazide) vs β-blockers (atenolol, metoprolol or pindolol)	outcomes in patients ≥60 years of age with HTN			Secondary: Not reported
Sundström et al.[75] (2023) Amlodipine 10 mg vs candesartan 16 mg vs lisinopril 20 mg vs HCTZ 25 mg Half doses given weeks 1 and 2 of each treatment period, and full doses weeks 3 through 9	DB, PRO, XO, RCT Patients aged 40 to 75 years previously diagnosed with HTN, with SBP 140 to 159 mmHg within a five-year period prior to the start of the trial and SBP 140 to 179 mm Hg and DBP ≤109 mm Hg at the randomization visit Patients were pharmacologically untreated or used BP-lowering monotherapy at the inclusion visit	N=280 Six treatment periods, each being 7 to 9 weeks in duration, after a 2 week washout period; 1-week washout periods between each treatment period	Primary: Ambulatory daytime SBP at the end of each treatment period Secondary: Not reported	Primary: Participants had higher BP when taking HCTZ than when taking other treatments, when taking amlodipine compared with lisinopril, and when taking candesartan compared with lisinopril The blood pressure response to different treatments varied considerably between individuals (P<0.001), specifically for the choices of lisinopril vs hydrochlorothiazide, lisinopril vs amlodipine, candesartan vs hydrochlorothiazide, and candesartan vs amlodipine. On average, personalized treatment had the potential to provide an additional 4.4 mm Hg–lower systolic blood pressure. Secondary: Not reported
Baguet et al.[76] (2007) Antihypertensive drugs (enalapril, ramipril,	MA Patients greater than 18 years of age with mild or moderate essential HTN (SBP	N=10,818 8 to 12 weeks	Primary: Weighted average reductions in SBP and DBP Secondary:	Primary: Data did not reflect outcomes from direct, head-to-head comparative trials or formal comparisons between drugs. Diuretics (-19.2 mm Hg; 95% CI, -20.3 to -18.0), calcium channel blockers (-16.4 mm Hg; 95% CI, -17.0 to -15.8) and ACE inhibitors (-15.6 mm Hg; 95% CI, -17.6 to -13.6) produced the greatest reductions in SBP from baseline (P values not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
trandolapril, candesartan, irbesartan, losartan, olmesartan, telmisartan, valsartan, HCTZ, indapamide SR*, atenolol, amlodipine, lercanidipine*, manidipine*, enalapril, ramipril, trandolapril, and aliskiren) Drugs were used as monotherapy, either at a fixed daily dosage or in increasing dosages. Although cicletanine*, furosemide and spironolactone were considered for inclusion, none of the trials relating to these agents satisfied all inclusion criteria.	140 to 179 mm Hg and/or DBP 90 to 109 mm Hg)		Not reported	The magnitude of DBP reductions were generally similar among all drug classes; however, the greatest reductions in DBP from baseline were observed with the β-blocker, atenolol (-11.4 mm Hg; 95% CI, -12.0 to -10.9), calcium channel blockers (-11.4 mm Hg; 95% CI, -11.8 to -11.1) and diuretics (-11.1 mm Hg; 95% CI, -11.7 to -10.5) (P values were not reported). The weighted average reduction of SBP and DBP for each drug class were as follows: Diuretics: -19.2 (95% CI, -20.3 to -18.0) and -11.1 mm Hg (95% CI, -11.7 to -10.5), respectively. β-blockers: -14.8 (95% CI, -15.9 to -13.7) and -11.4 mm Hg (95% CI, -12.0 to -10.9), respectively. Calcium channel blockers: -16.4 (95% CI, -17.0 to -15.8) and -11.4 mm Hg (95% CI, -11.8 to -11.1), respectively. ACE inhibitors: -15.6 (95% CI, -17.6 to -13.6) and -10.8 mm Hg (95% CI, -11.9 to -9.7), respectively. ARBs: -13.2 (95% CI, -13.6 to -12.9) and -10.3 mm Hg (95% CI, -10.5 to -10.1), respectively. Renin inhibitor: -13.5 (95% CI, -14.2 to -12.9) and -11.3 mm Hg (95% CI, -11.7 to -10.9), respectively. Secondary: Not reported
Lindholm et al.[77] (2005) Other	MA 13 RCTs evaluating the treatment of	N=105,951 2.1 to 10.0 years	Primary: Stroke, MI, all-cause mortality	Primary: The RR of stroke was 16% higher with β-blocker therapy than for the comparator therapies (RR, 1.16; 95% CI, 1.04 to 1.30; P=0.009). The RR of stroke was the highest with atenolol (26% higher) compared to other

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
antihypertensive therapies (amiloride, amlodipine, bendro-flumethiazide*, captopril, diltiazem, enalapril, felodipine, HCTZ, isradipine, lacidipine, lisinopril, losartan, or verapamil) or placebo vs β-blocker therapy (atenolol, metoprolol, oxprenolol*, pindolol, or propranolol)	primary HTN with a β-blocker as first-line treatment (in ≥50% of all patients in one treatment group) and outcome data for all-cause mortality, cardiovascular morbidity or both		Secondary: Not reported	non β-blockers (RR, 1.26%; 95% CI, 15 to 38; P<0.0001). The relative risk of MI was 2% higher for β- blocker therapy than for the comparator therapies (RR, 1.02; 95% CI, 0.93 to 1.12), which was not significant (P value not reported). The RR of all-cause mortality was 3% higher for β-blocker therapy than for the comparator therapies (RR, 1.16; 95% CI, 0.99 to 1.08; P=0.14). Secondary: Not reported
Hilleman et al.[78] (1999) Monotherapy (atenolol, HCTZ, captopril, enalapril, lisinopril, amlodipine,	MA (82 trials) Patients with mild-to-moderate essential HTN	N=not reported ≥4 weeks	Primary: Absolute change in supine DBP from baseline Secondary: Percent of patients who achieved blood pressure control, safety	Primary: The mean absolute decrease in supine DBP ranged from 9.7 to 13.3 mm Hg with verapamil showing the greatest effect and captopril the least. When studies were weighted by sample size, amlodipine and benazepril, atenolol, lisinopril, and verapamil showed the greatest blood pressure effect. Secondary: The average percentage of patients defined as controlled after treatment varied from 53.5 to 79.0%, with amlodipine and benazepril (74.3%) and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
diltiazem, nifedipine, verapamil) vs amlodipine-benazepril (fixed-dose combination)				lisinopril (79.0%) showing the highest percentage control (P=0.096). The incidence of adverse events ranged from 12.1 to 41.8%, with lisinopril and verapamil showing the lowest incidences (12.1% and 14.1%, respectively) and nifedipine the highest incidence. Lisinopril demonstrated significantly less overall side effects compared to nifedipine (P=0.030). Nifedipine demonstrated a higher withdrawal rate due to side effects compared to atenolol, HCTZ, enalapril, amlodipine, and diltiazem (P=0.002). Although amlodipine and benazepril had the lowest rate of withdrawals due to adverse events, lack of significant change was due to the low number of cohorts available for analysis.
Wiysonge et al.[79] (2007) Other antihypertensive therapies (i.e., placebo, diuretics, calcium channel blockers, or renin-angiotensin system inhibitors) vs β-blockers (atenolol, metoprolol, oxprenolol*, or propranolol)	MA 13 RCTs evaluating patients ≥18 years of age with HTN	N=91,561 Duration varied	Primary: All-cause mortality Secondary: Stroke, CHD, cardiovascular death, total cardiovascular disease, adverse reactions	Primary: There was not a significant difference observed in all-cause mortality between β-blocker therapy and placebo (RR, 0.99; 95% CI, 0.88 to 1.11; P value not reported), diuretics (RR, 1.04; 95% CI, 0.91 to 1.19; P value not reported) or renin-angiotensin system inhibitors (RR, 1.10; 95% CI, 0.98 to 1.24; P value not reported). There was a significantly higher rate in all-cause mortality with β-blocker therapy compared to calcium channel blockers (RR, 1.07; 95% CI, 1.00 to 1.14; P=0.04). Secondary: There was a significant decrease in stroke observed with β-blocker therapy compared to placebo (RR, 0.80; 95% CI, 0.66 to 0.96). Also there was a significant increase in stroke with β-blocker therapy compared to calcium channel blockers (RR, 1.24; 95% CI, 1.11 to 1.40) and renin-angiotensin system inhibitors (RR, 1.30; 95% CI, 1.11 to 1.53), but there was no difference observed compared to diuretics (RR, 1.17; 95% CI, 0.65 to 2.09). CHD risk was not significantly different between β-blocker therapy and placebo (RR, 0.93; 95% CI, 0.81 to 1.07]), diuretics (RR, 1.12; 95% CI, 0.82 to 1.54), calcium channel blockers (RR, 1.05; 95% CI, 0.96 to 1.15) or renin-angiotensin system inhibitors (RR, 0.90; 95% CI, 0.76 to 1.06). The risk of total cardiovascular disease was lower with β-blocker therapy compared to placebo (RR, 0.88; 95% CI, 0.79 to 0.97). The effect of β-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				blocker therapy on cardiovascular disease was significantly worse than that of calcium channel blockers (RR, 1.18; 95% CI, 1.08 to 1.29), but was not significantly different from that of diuretics (RR, 1.13; 95% CI, 0.99 to 1.28) or renin-angiotensin system inhibitors (RR, 1.00; 95% CI, 0.72 to 1.3). There was a significantly higher rate of discontinuation due to side effects with β-blocker therapy compared to diuretics (RR, 1.86; 95% CI, 1.39 to 2.50) and renin-angiotensin system inhibitors (RR, 1.41; 95% CI, 1.29 to 1.54), but there was no significant difference compared to calcium channel blockers (RR, 1.20; 95% CI, 0.71 to 2.04). Actual side effects were not reported.

*Agent not available in the United States.
Drug regimen abbreviations: BID=twice daily, QD=once daily, SR=sustained-release
Study Design abbreviations: AC=active comparator, BE=blinded endpoint, DB=double blind, DD=double dummy, MA=meta analysis, MC=multicenter, OL=open label, PC=placebo controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, SB=single blind, XO=cross over
Miscellaneous abbreviations: ACE inhibitors=angiotensin converting enzyme inhibitors, ABPM=ambulatory blood pressure monitoring, BSA=body surface area, CHD=coronary heart disease, CHF=congestive heart failure, CI=confidence interval, DBP=diastolic blood pressure, HCTZ=hydrochlorothiazide, HDL-C=high-density lipoprotein cholesterol, HR=hazard ratio, HTN=hypertension, KCl=potassium chloride, MI=myocardial infarction, NNT=number needed to treat, NYHA=New York Heart Association, OR=odds ratio, PVD=peripheral arterial disease, RR=relative risk, SBP=systolic blood pressure, TC=total cholesterol, TG=triglyceride, TIA=transient ischemic attack, WHO=World Health Organization, WMD=weighted mean difference

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 9. Relative Cost of the Thiazide Diuretics

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Chlorothiazide	injection*, suspension	Diuril®	$$	$$
HCTZ	capsule, tablet	N/A	N/A	$

*Generic is available in at least one dosage form or strength.
HCTZ=hydrochlorothiazide, N/A=Not available

X. Conclusions

The thiazide diuretics are approved for the treatment of hypertension and edema due to renal dysfunction. They are also approved as adjunctive therapy for the management of edema associated with congestive heart failure, hepatic cirrhosis, as well as corticosteroid and estrogen therapy.[1-3] All of the agents are available in a generic formulation.

Guidelines recommend the use of diuretics and sodium restriction for the management of ascites due to cirrhosis. Spironolactone is recommended as first-line therapy, either as monotherapy or in combination with furosemide. Amiloride or eplerenone are alternative treatment options in patients experiencing gynecomastia with spironolactone.[17]

For the treatment of chronic heart failure, guidelines recommend the use of diuretics in all patients who have evidence of volume overload. Loop diuretics are generally recommended as initial therapy in patients with left

ventricular dysfunction. For those with persistent fluid retention despite treatment with a loop diuretic, a thiazide diuretic or metolazone may be added to the regimen. In patients with normal left ventricular function, either a thiazide diuretic or loop diuretic may be used as initial therapy to manage fluid overload.[6,7]

There are several published guidelines on the treatment of hypertension. Thiazide-type diuretics are frequently recommended as initial therapy in patients with uncomplicated hypertension.[8-14] According to the National Heart, Lung, and Blood Institute's Eighth Report of The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8), thiazide-type diuretics should be utilized first-line for most patients with hypertension, either alone or in combination with another hypertensive from a different medication class (e.g., ACE inhibitors, ARBs, β-blockers, calcium channel blockers).[8] Several guidelines consistently recommend that the selection of an antihypertensive agent be based on compelling indications for use.[8-16] Most patients will require more than one antihypertensive medication to achieve blood pressure goals.[8-14]

In clinical trials, the thiazide diuretics have been shown to effectively lower blood pressure.[22-79] There were no studies found in the medical literature that directly compared the efficacy and safety of the thiazide diuretics for the treatment of hypertension.

There is insufficient evidence to support that one brand thiazide diuretic is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand thiazide diuretics within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand thiazide diuretic is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Thiazide-Like Diuretics
AHFS Class 402824
May 8, 2024

I. Overview

The thiazide-like diuretics are approved for the treatment of edema and hypertension.[1-2] They inhibit sodium reabsorption in the distal convoluted tubule of the nephron. This results in an initial modest reduction in plasma volume and cardiac output. However, long-term maintenance of decreased blood pressure has been shown to be associated with partial reversal of the hemodynamic changes as plasma volume and cardiac output return to baseline. Although thiazide-like diuretics are pharmacologically similar to thiazide diuretics, there are chemical differences in the molecular structure that differentiate these agents. Indapamide may produce an independent vascular action, which results in a reduction in total peripheral resistance. Metolazone may produce diuresis in patients with glomerular filtration rates below 20 mL/minute.[1-4]

The thiazide-like diuretics that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All of the agents are available in a generic formulation. This class was last reviewed in May 2022.

Table 1. Thiazide-Like Diuretics Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Chlorthalidone	tablet*	Thalitone®	chlorthalidone
Indapamide	tablet*	N/A	indapamide
Metolazone	tablet*	N/A	metolazone

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List
N/A=Not available

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the thiazide-like diuretics are summarized in Table 2.

Table 2. Treatment Guidelines Using the Thiazide-Like Diuretics

Clinical Guideline	Recommendation(s)
American Heart Association/American College of Cardiology/ Heart Failure Society of America: **2022 AHA/ACC /HFSA Guideline for the Management of Heart Failure (2022)[5]**	<u>Treatment of Stage A heart failure (HF)</u> • Hypertension should be controlled in accordance with guideline-directed medication therapy for hypertension to prevent symptomatic HF. (LoE: A) • In patients with type 2 diabetes and either established CVD or at high cardiovascular risk, SGLT-2 inhibitors should be used to prevent hospitalizations for HF. (LoE: A) • In the general population, healthy lifestyle habits such as regular physical activity, maintaining normal weight, healthy dietary patterns, and avoiding smoking are helpful to reduce future risk of HF. (LoE: B) • Patients at risk of developing HF, natriuretic peptide biomarker-based screening followed by team-based care, including a cardiovascular specialist optimizing therapy, can be useful to prevent the development of LV dysfunction (systolic or diastolic) or new-onset HF. (LoE: B) <u>Treatment of Stage B heart failure</u> • In patients with LVEF≤40%, ACE inhibitors should be used to prevent HF and reduce mortality. (LoE: A) • In patients with a recent or remote history of MI or ACS, statins should be used to prevent symptomatic HF and adverse cardiovascular events. (LoE: A)

Clinical Guideline	Recommendation(s)
	• In patients with a recent MI and LVEF≤40% who are intolerant to ACE inhibitors, ARB should be used to prevent symptomatic HF and reduce mortality. (LoE: B) • In patients with a recent or remote history of MI or ACS and LVEF≤40%, evidence-based beta blockers should be used to reduce mortality. (LoE: B) • In patients who are at least 40 days post-MI with LVEF ≤30% and NYHA class I symptoms while receiving guideline-directed medication therapy and have reasonable expectation of meaningful survival for greater than one year, an implantable cardioverter-defibrillator is recommended for primary prevention of sudden cardiac death to reduce total mortality. (LoE: B) • In patients with LVEF ≤40%, beta blockers should be used to prevent symptomatic HF. (LoE: C) • In patients with LVEF ≤50%, thiazolidinediones should not be used because they increase the risk of HF, including hospitalizations. (LoE: B) • In patients with LVEF ≤50%, nondihydropyridine calcium channel blockers with negative inotropic effects may be harmful. (LoE: C) <u>Treatment for Stage C Heart Failure with Reduced Ejection Fraction (HFrEF)</u> • For patients with stage C HF, avoiding excessive sodium intake is reasonable to reduce congestive symptoms. (LoE: C) • In patients with HF who have fluid retention, diuretics are recommended to relieve congestion, improve symptoms, and prevent worsening HF. (LoE: B) • For patients with HF and congestive symptoms, addition of a thiazide (e.g., metolazone) to treatment with a loop diuretic should be reserved for patients who do not respond to moderate or high dose loop diuretics to minimize electrolyte abnormalities. (LoE: B) • In patients with HFrEF and NYHA class II to III symptoms, the use of an ARNI is recommended to reduce morbidity and mortality. (LoE: A) • In patients with previous or current symptoms of chronic HFrEF, the use of an ACE inhibitor is beneficial to reduce morbidity and mortality when the use of an ARNI is not feasible. (LoE: A) • In patients with previous or current symptoms of chronic HFrEF, who are intolerant to an ACE inhibitor because of cough or angioedema, and when the use of an ARNI is not feasible, the use of an ARB is recommended to reduce morbidity and mortality. (LoE: A) • In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality. (LoE: B) • ARNIs should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor. (LoE: B) • ARNI or ACE inhibitors should not be administered in patients with a history of angioedema. (LoE: C) • In patients with HFrEF, with current or previous symptoms, use of one of the three β-blockers proven to reduce mortality (e.g., bisoprolol, carvedilol, sustained-release metoprolol succinate) is recommended to reduce mortality and hospitalizations. (LoE: A) • In patients with HFrEF and NYHA class II to IV symptoms, a mineralocorticoid receptor antagonist (spironolactone or eplerenone) is recommended to reduce morbidity and mortality, if eGFR is >30 mL/min/1.73 m^2 and serum potassium is <5.0 mEq/L. Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely followed thereafter to minimize risk of hyperkalemia and renal insufficiency. (LoE: A) • In patients taking a mineralocorticoid receptor antagonist whose serum potassium cannot be maintained at <5.5 mEq/L, mineralocorticoid receptor antagonist should be discontinued to avoid life threatening hyperkalemia. (LoE: B) • In patients with symptomatic chronic HFrEF, SGLT-2 an inhibitor is

Clinical Guideline	Recommendation(s)
	recommended to reduce hospitalization for HF and cardiovascular mortality, irrespective of the presence of type 2 diabetes. (LoE: A) • The combination of hydralazine and isosorbide dinitrate is recommended to improve symptoms and reduce morbidity and mortality for patients self-identified as African Americans with NYHA class III to IV HFrEF receiving optimal therapy. (LoE: A) • In patients with current or previous symptomatic HFrEF who cannot be given first-line agents, such as an ARNI, ACE inhibitor or ARB because of drug intolerance or renal insufficiency, a combination of hydralazine and isosorbide dinitrate might be considered to reduce morbidity and mortality. (LoE: C) • In patients with HF class II to IV symptoms, omega-3 polyunsaturated fatty acid supplementation may be reasonable to use as adjunctive therapy to reduce mortality and cardiovascular hospitalizations. (LoE: B) • In patients with chronic HFrEF without specific indication (e.g., venous thromboembolism, atrial fibrillation, a previous thromboembolic event, or a cardioembolic source, anticoagulation is not recommended. (LoE: B) • Dihydropyridine and non-dihydropyridine calcium channel blockers are not recommended for patients with HFrEF. (LoE: A) • In patients with HFrEF, vitamins, nutritional supplements, and hormonal therapy are not recommended other than to correct specific deficiencies. (LoE: B) • In patients with HFrEF, class IC antiarrhythmic medication and dronedarone may increase risk of mortality. (LoE: A) • In patients with HFrEF, thiazolidinediones increase the risk of worsening HF symptoms and hospitalizations. (LoE: A) • In patients with type 2 diabetes and high cardiovascular risk, the DPP-4 inhibitors, saxagliptin and alogliptin, increase the risk of HF hospitalization and should be avoided in patients with HF. (LoE: B) • In patients with HFrEF, nonsteroidal anti-inflammatory drugs worsen HF symptoms and should be avoided or withdrawn whenever possible. (LoE: B) • For patients with symptomatic (NYHA class II to III) stable chronic HFrEF (LVEF ≤35%) who are receiving guideline-directed medical therapy, including a maximally tolerated dose of a beta blocker, and who are in sinus rhythm with a heart rate of ≥70 beats per minute at rest, ivabradine can be beneficial to reduce HF hospitalizations and cardiovascular death. (LoE: B) • In patients with symptomatic HFrEF despite guideline-directed medical therapy or who are unable to tolerate guideline-directed medical therapy, digoxin might be considered to decrease hospitalizations for HF. (LoE: B) • In select high-risk patients with HFrEF and recent worsening of HF already on guideline-directed medical therapy, an oral soluble guanylate cyclase stimulator (vericiguat) may be considered to reduce HF hospitalization and cardiovascular death. (LoE: B) <u>Pharmacological treatment for Stage C HF with mildly reduced EF and improved EF</u> • In patients with HF with mildly reduced EF, SGLT-2 inhibitors can be beneficial in decreasing HF hospitalizations and cardiovascular mortality. (LoE: B) • Among patients with current or previous symptomatic HF with mildly reduced EF (LVEF, 41 to 49%), use of evidence-based beta blockers for HFrEF, ARNI, ACE inhibitor or ARB, and mineralocorticoid receptor antagonists may be considered to reduce the risk of HF hospitalization and cardiovascular mortality, particularly among patients with LVEF on the lower end of this spectrum. (LoE: B) • In patients with HF with improved EF after treatment, guideline-directed medical therapy should be continued to prevent relapse of HF and LV dysfunction, even in patients who may become asymptomatic. (LoE: B) <u>Pharmacological treatment for Stage C HF with preserved EF (HFpEF)</u>

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	• Patients with hypertension and HFpEF should have medication titrated to attain blood pressure targets in accordance with published clinical practice guidelines to prevent morbidity. (LoE: C) • SGLT-2 inhibitors can be beneficial in decreasing HF hospitalizations and cardiovascular mortality. (LoE: B) • In patients with HFpEF, the use of a mineralocorticoid receptor antagonist, ARB, or ARNI may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum. (LoE: B) • Routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or quality of life in patients with HFpEF is ineffective. (LoE: B) <u>Treatment of Stage D (advanced/refractory) HF</u> • For patients with advanced HF and hyponatremia, the benefit of fluid restriction to reduce congestive symptoms is uncertain. (LoE: C) • Continuous intravenous inotropic support is reasonable as "bridge therapy" in patients with HF (Stage D) refractory to guideline-directed medical therapy and device therapy who are eligible for and awaiting mechanical circulatory support or cardiac transplantation. (LoE: B) • In select patients with HF Stage D, despite optimal guideline-directed medical therapy and device therapy who are ineligible for either mechanical circulatory support or cardiac transplantation, continuous intravenous inotropic support may be considered as palliative therapy for symptom control and improvement in functional status. (LoE: B) • Long-term use of either continuous or intermittent, intravenous inotropic agents, for reasons other than palliative care or as a bridge to advanced therapies, is potentially harmful. (LoE: B)
European Society of Cardiology: **Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (2021)[6]**	<u>Pharmacological treatments indicated in patients with (NYHA Class II-IV) heart failure with reduced ejection fraction</u> • An ACE inhibitor is recommended, in addition to a β-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death. • A mineralocorticoid receptor antagonist (MRA) is recommended for patients with HFrEF, who remain symptomatic despite treatment with an ACE inhibitor and a β-blocker, to reduce the risk of HF hospitalization and death. • Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death. Dapagliflozin or empagliflozin are recommended, in addition to optimal medical therapy with an ACE-I/ARNI, a β-blocker and an MRA, for patients with HFrEF regardless of diabetes status. • Sacubitril-valsartan is recommended as a replacement for an ACE inhibitor to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE inhibitor, a β-blocker, and a mineralocorticoid receptor antagonist. • Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion. • Ivabradine should be considered to reduce the risk of HF hospitalization or cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm despite treatment with an evidence-based dose of β-blocker (or maximum tolerated dose below that), ACE inhibitor (or ARB), and a mineralocorticoid receptor antagonist (or ARB). • Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm who are unable to tolerate or have contraindications for a β-blocker. Patients should also receive an ACE inhibitor (or ARB) and a mineralocorticoid receptor antagonist (or ARB). • An ARB is recommended to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients unable to tolerate an ACE inhibitor

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	(patients should also receive a β-blocker and mineralocorticoid receptor antagonist). • An ARB may be considered to reduce the risk of HF hospitalization and death in patients who are symptomatic despite treatment with a β-blocker who are unable to tolerate a mineralocorticoid receptor antagonist. • Vericiguat may be considered in patients in NYHA class II-IV who have had worsening HF despite treatment with an ACE-I (or ARNI), a β-blocker and an MRA to reduce the risk of CV mortality or HF hospitalization. • Hydralazine and isosorbide dinitrate should be considered in self-identified black patients with LVEF ≤35% or with an LVEF <45% combined with a dilated LV in NYHA Class III–IV despite treatment with an ACE-I a β-blocker and a mineralocorticoid receptor antagonist to reduce the risk of HF hospitalization and death. • Hydralazine and isosorbide dinitrate may be considered in symptomatic patients with HFrEF who can tolerate neither an ACE inhibitor nor an ARB (or they are contraindicated) to reduce the risk of death. • Digoxin is a treatment with less-certain benefits and may be considered in symptomatic patients in sinus rhythm despite treatment with an ACE inhibitor (or ARB), a β-blocker and a mineralocorticoid receptor antagonist, to reduce the risk of hospitalization (both all-cause and HF-hospitalizations). <u>Recommendations for treatment of patients with (NYHA class II-IV) heart failure with mildly reduced ejection fraction (HFmrEF)</u> • Diuretics are recommended in patients with congestion and HFmrEF in order to alleviate symptoms and signs. • An ACE inhibitor may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • An ARB may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • A β-blocker may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • An MRA may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. • Sacubitril/valsartan may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. <u>Recommendations for treatment of patients with heart failure with preserved ejection fraction (HFpEF)</u> • It is recommended to screen patients with HFpEF for both cardiovascular and noncardiovascular comorbidities, which, if present, should be treated provided safe and effective interventions exist to improve symptoms, well-being and/or prognosis. • Diuretics are recommended in congested patients with HFpEF in order to alleviate symptoms and signs. <u>Recommendations for the primary prevention of heart failure in patients with risk factors for its development</u> • Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life. • Treatment with statins is recommended in patients at high risk of CV disease or with CV disease in order to prevent or delay the onset of HF, and to prevent HF hospitalizations. • SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with diabetes at high risk of CV disease or with CV disease in order to prevent HF hospitalizations.

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	• Counselling against sedentary habit, obesity, cigarette smoking, and alcohol abuse is recommended to prevent or delay the onset of HF. <u>Recommendations for the initial management of patients with acute heart failure – pharmacotherapy</u> • Intravenous loop diuretics are recommended for all patients with acute HF admitted with signs/symptoms of fluid overload to improve symptoms. It is recommended to regularly monitor symptoms, urine output, renal function and electrolytes during use of intravenous diuretics. • Combination of a loop diuretic with thiazide type diuretic should be considered in patients with resistant oedema who do not respond to an increase in loop diuretic doses. • In patients with acute HF and SBP >110 mmHg, intravenous vasodilators may be considered as initial therapy to improve symptoms and reduce congestion. • Inotropic agents may be considered in patients with SBP <90 mmHg and evidence of hypoperfusion who do not respond to standard treatment, including fluid challenge, to improve peripheral perfusion and maintain end-organ function. • Inotropic agents are not recommended routinely, due to safety concerns, unless the patient has symptomatic hypotension and evidence of hypoperfusion. • A vasopressor, preferably norepinephrine, may be considered in patients with cardiogenic shock to increase blood pressure and vital organ perfusion. • Thromboembolism prophylaxis (e.g. with LMWH) is recommended in patients not already anticoagulated and with no contraindication to anticoagulation, to reduce the risk of deep venous thrombosis and pulmonary embolism. • Routine use of opiates is not recommended, unless in selected patients with severe/intractable pain or anxiety.
Eighth Joint National Committee (JNC 8): **2014 Evidence-based Guideline for the Management of High Blood Pressure in Adults (2014)**[7]	• Pharmacologic treatment should be initiated in patients ≥60 years of age to lower blood pressure at systolic blood pressure ≥150 mm Hg or diastolic blood pressure ≥90 mm Hg and to a goal systolic blood pressure <150 mm Hg and goal diastolic blood pressure <90 mm Hg. Adjustment of treatment is not necessary if treatment results in lower blood pressure and treatment is well tolerated and without adverse effects on health or quality of life. • In patients <60 years of age, pharmacologic treatment should be initiated to lower blood pressure at diastolic blood pressure ≥90 mm Hg to a goal diastolic blood pressure <90 mm Hg. • In patients <60 years of age, pharmacologic treatment should be initiated to lower blood pressure at systolic blood pressure ≥150 mm Hg to a goal diastolic blood pressure <140 mm Hg. • For patients ≥18 years of age with chronic kidney disease or diabetes, pharmacologic treatment should be initiated to lower blood pressure at systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg and to a goal systolic blood pressure <140 mm Hg and goal diastolic blood pressure <90 mm Hg. • Initial antihypertensive treatment for the general nonblack population, including those with diabetes, should include thiazide-type diuretic, calcium channel blocker (CCB), ACE inhibitor, or ARB. • Initial antihypertensive treatment for the general black population, including those with diabetes, should include thiazide-type diuretic or CCB. • For patients ≥18 years of age with chronic kidney disease regardless of race or diabetes status, initial (or add-on) treatment should include an ACE inhibitor or ARB to improve kidney outcomes. • The main goal of antihypertensive treatment is to attain and maintain goal blood pressure. • If goal blood pressure is not attained within a month of treatment, the dose of the initial drug should be increased or second drug from the thiazide-type diuretic,

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	CCB, ACE inhibitor, or ARB classes should be added. • If goal is not achieved with two drugs, a third drug from the thiazide-type diuretic, CCB, ACE inhibitor, or ARB classes should be added. • An ACE inhibitor and ARB should not be used together. • Antihypertensive classes can be used if the patient is unable to achieve goal blood pressure with three agents or had a contraindication to a preferred class. • If blood pressure is not able to be achieved or in complicated patients, referral to a hypertension specialist may be indicated.
International Society of Hypertension: **Global Hypertension Practice Guidelines (2020)[8]**	<u>Lifestyle modifications</u> • Lifestyle modification is the first line of antihypertensive treatment. • Salt reduction: Reduce salt added when preparing foods, and at the table. Avoid or limit consumption of high salt foods such as soy sauce, fast foods and processed food including breads and cereals high in salt. • Healthy diet: Eating a diet that is rich in whole grains, fruits, vegetables, polyunsaturated fats and dairy products and reducing food high in sugar, saturated fat and trans fats, such as the DASH diet. • Healthy drinks: Moderate consumption of coffee, green and black tea. Other beverages that can be beneficial include karkadé (hibiscus) tea, pomegranate juice, beetroot juice and cocoa. • Moderation of alcohol consumption: The recommended daily limit for alcohol consumptions is 2 standard drinks for men and 1.5 for women (10 g alcohol/standard drink). Avoid binge drinking. • Weight reduction: Body weight control is indicated to avoid obesity. Particularly abdominal obesity should be managed. Ethnic-specific cut-offs for BMI and waist circumference should be used. Alternatively, a waist-to-height ratio <0.5 is recommended for all populations. • Smoking cessation: Smoking is a major risk factor for cardiovascular disease (CVD), COPD and cancer. Smoking cessation and referral to smoking cessation programs are advised. • Regular physical activity: Studies suggest that regular aerobic and resistance exercise may be beneficial for both the prevention and treatment of hypertension. Moderate intensity aerobic exercise (walking, jogging, cycling, yoga, or swimming) for 30 minutes on five to seven days per week Strength training also can help reduce blood pressure. Performance of resistance/strength exercises on two to three days per week. • Reduce stress and induce mindfulness: Stress should be reduced and mindfulness or meditation introduced into the daily routine. • Reduce exposure to air pollution and cold temperature: Evidence from studies support a negative effect of air pollution on blood pressure in the long-term. <u>Pharmacological Treatment</u> • Ideal characteristics of drug treatment o Treatments should be evidence-based in relation to morbidity/mortality prevention. o Use a once-daily regimen which provides 24-hour blood pressure control. o Treatment should be affordable and/or cost-effective relative to other agents. o Treatments should be well-tolerated. o Evidence of benefits of use of the medication in populations to which it is to be applied. • General scheme for drug treatment o Lifestyle modification is the first line of antihypertensive treatment. o Grade 1 hypertension (BP 140 to 159/ 90 to 99): Immediate drug treatment in high-risk patients or those with CVD, chronic kidney disease (CKD), diabetes mellitus (DM), or hypertension-mediated organ damage

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	(HMOD). Drug treatment after three to six months of lifestyle intervention if BP still not controlled in low to moderate risk patients. o Grade 2 hypertension (BP ≥160/100): Immediate drug treatment in all patients. • Core drug-treatment strategy o Step 1: Dual low-dose combination (ACE inhibitor or ARB plus dihydropyridine-calcium channel blockers (DHP-CCB)); consider monotherapy in low-risk grade 1 hypertension or in very old (≥80 years) or frail patients; consider ACE/ARB plus thiazide-like diuretic in post-stroke, very elderly, incipient HF, or CCB intolerance; consider ACE/ARB plus DHP-CCB or DHP-CCB plus thiazide-like diuretics in black patients. o Step 2: Dual full-dose combination (ACE inhibitor or ARB plus DHP-CCB); consider monotherapy in low-risk grade 1 hypertension or in very old (≥80 years) or frail patients; consider ACE/ARB plus thiazide-like diuretic in post-stroke, very elderly, incipient HF, or CCB intolerance. o Step 3: Triple combination (ACE/ARB plus DHP-CCB plus thiazide-like diuretic). o Step 4, resistant hypertension: triple combination plus spironolactone or other drug, alternatives include amiloride, doxazosin, eplerenone, clonidine, or β-blocker. Caution with spironolactone or other potassium sparing diuretics when estimated GFR <45 mL/min/1.73m^2 or K+ >4.5 mmol/L. o Consider β-blockers at any treatment step when there is a specific indications for their use, e.g., heart failure, angina, post-MI, atrial fibrillation, or younger women planning pregnancy or pregnant.
Hypertension Canada: **2020 Guidelines for the Prevention, Diagnosis, Risk Assessment, and Treatment of Hypertension in Adults and Children (2020)[9]**	<u>Indications for drug therapy for adults with hypertension without compelling indications for specific agents</u> • Antihypertensive therapy should be prescribed for average diastolic blood pressure (DBP) measurements of ≥100 mmHg or average systolic blood pressure (SBP) measurements of ≥160 mmHg in patients without macrovascular target organ damage or other cardiovascular risk factors. • Antihypertensive therapy should be strongly considered for average DPB readings ≥90 mmHg or for average SBP readings ≥140 mmHg in the presence of macrovascular target organ damage or other independent cardiovascular risk factors. • For high-risk patients, aged 50 years or older, with SBP levels ≥130 mmHg, intensive management to target a SBP <120 mmHg should be considered. Patient selection for intensive management is recommended and caution should be taken in certain high-risk groups. <u>Indications for drug therapy for adults with diastolic and with or without systolic hypertension</u> • Initial therapy should be with either monotherapy or single pill combination (SPC). o Recommended monotherapy choices are: ▪ A thiazide/thiazide-like diuretic, with longer-acting diuretics preferred; ▪ A β-blocker (in patients <60 years of age); ▪ An angiotensin-converting enzyme (ACE) inhibitor (in nonblack patients); ▪ An angiotensin receptor blocker (ARB); or ▪ A long-acting calcium channel blocker (CCB). o Recommended SPC choices are those in which an ACE inhibitor is combined with a CCB, ARB with a CCB, or ACE inhibitor or ARB with a diuretic. o Hypokalemia should be avoided in patients treated with thiazide/thiazide-like

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	diuretic monotherapy. • Additional antihypertensive drugs should be used if target BP levels are not achieved with standard-dose monotherapy. Add-on drugs should be chosen from first-line choices. Useful choices include a thiazide/thiazide-like diuretic or CCB with either: ACE inhibitor, ARB, or β-blocker. Caution should be exercised in combining a nondihydropyridine CCB and a β-blocker. The combination of an ACE inhibitor and an ARB is not recommended. • If BP is still not controlled with a combination of two or more first-line agents, or there are adverse effects, other antihypertensive drugs may be added. • Possible reasons for poor response to therapy should be considered. • α-Blockers are not recommended as first-line agents for uncomplicated hypertension; β-blockers are not recommended as first-line therapy for uncomplicated hypertension in patients ≥60 years of age; and ACE inhibitors are not recommended as first-line therapy for uncomplicated hypertension in black patients. However, these agents may be used in patients with certain comorbid conditions or in combination therapy. <u>Indications for drug therapy for adults with isolated systolic hypertension</u> • Initial therapy should be single-agent therapy with a thiazide/thiazide-like diuretic, a long-acting dihydropyridine CCB, or an ARB. If there are adverse effects, another drug from this group should be substituted. Hypokalemia should be avoided in patients treated with thiazide/thiazide-like diuretic monotherapy. • Additional antihypertensive drugs should be used if target BP levels are not achieved with standard-dose monotherapy. Add-on drugs should be chosen from first-line options. • If BP is still not controlled with a combination of two or more first-line agents, or there are adverse effects, other classes of drugs (such as α-blockers, ACE inhibitors, centrally acting agents, or nondihydropyridine CCBs) may be combined or substituted. • Possible reasons for poor response to therapy should be considered. • α-Blockers are not recommended as first-line agents for uncomplicated isolated systolic hypertension; and β-blockers are not recommended as first-line therapy for isolated systolic hypertension in patients ≥60 years of age. However, both agents may be used in patients with certain comorbid conditions or in combination therapy. <u>Guidelines for hypertensive patients with coronary artery disease (CAD)</u> • For most hypertensive patients with CAD, an ACE inhibitor or ARB is recommended. • For hypertensive patients with CAD, but without coexisting systolic heart failure, the combination of an ACE inhibitor and ARB is not recommended. • For high-risk hypertensive patients, when combination therapy is being used, choices should be individualized. The combination of an ACE inhibitor and a dihydropyridine CCB is preferable to an ACE inhibitor and a thiazide/thiazide-like diuretic in selected patients. • For patients with stable angina pectoris but without previous heart failure, myocardial infarction, or coronary artery bypass surgery, either a β-blocker or CCB can be used as initial therapy. • Short-acting nifedipine should not be used. • When decreasing SBP to target levels in patients with established CAD (especially if isolated systolic hypertension is present), be cautious when the DBP is ≤60 mmHg because of concerns that myocardial ischemia might be exacerbated, especially in patients with left ventricular hypertrophy (LVH). <u>Guidelines for patients with hypertension who have had a recent myocardial infarction</u>

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	• Initial therapy should include a β-blocker as well as an ACE inhibitor.
	• An ARB can be used if the patient is intolerant of an ACE inhibitor.
	• CCBs may be used in patients after myocardial infarction when β-blockers are contraindicated or not effective. Nondihydropyridine CCBs should not be used when there is heart failure, evidenced by pulmonary congestion on examination or radiography.
	
	<u>Treatment of hypertension in association with heart failure</u>
	• In patients with systolic dysfunction (ejection fraction <40%), ACE inhibitors and β-blockers are recommended for initial therapy. Aldosterone antagonists (mineralocorticoid receptor antagonists) may be combined in treatment for patients with a recent cardiovascular hospitalization, acute myocardial infarction, elevated B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide level, or New York Heart Association (NYHA) Class II-IV symptoms. Careful monitoring for hyperkalemia is recommended when combining an aldosterone antagonist with ACE inhibitor or ARB treatment. Other diuretics are recommended as additional therapy if needed. Beyond considerations of BP control, doses of ACE inhibitors or ARBs should be titrated to those reported to be effective in trials unless adverse effects become manifest.
	• An ARB is recommended if ACE inhibitors are not tolerated.
	• A combination of hydralazine and isosorbide dinitrate is recommended if ACE inhibitors and ARBs are contraindicated or not tolerated.
	• For hypertensive patients whose BP is not controlled, an ARB may be combined with an ACE inhibitor and other antihypertensive drug treatment. Careful monitoring should be used if combining an ACE inhibitor and an ARB because of potential adverse effects such as hypotension, hyperkalemia, and worsening renal function. Additional therapies may also include dihydropyridine CCBs.
	• An angiotensin receptor-neprilysin inhibitor (ARNI) should be used in place of an ACE inhibitor or ARB for patients with HFrEF (<40%) who remain symptomatic despite treatment with appropriate dose of guideline directed HF therapy. Eligible patients must have a serum potassium <5.2 mmol/L, an eGFR ≤30 mL/min/1.73m^2 and close surveillance of serum potassium and creatinine.
	
	<u>Treatment of hypertension in association with stroke</u>
	• BP management in acute ischemic stroke (onset to 72 hours)
	  ○ Please refer to Stroke Best Practice recommendations.
	• BP management after acute ischemic stroke
	  ○ Strong consideration should be given to the initiation of antihypertensive therapy after the acute phase of a stroke or transient ischemic attack.
	  ○ After the acute phase of a stroke, BP-lowering treatment is recommended to a target of consistently <140/90 mmHg.
	  ○ Treatment with an ACE inhibitor and thiazide/thiazide-like diuretic combination is preferred.
	  ○ For patients with stroke, the combination of an ACE inhibitor and ARB is not recommended.
	• BP management in hemorrhagic stroke (onset to 72 hours)
	  ○ Please refer to Stroke Best Practice recommendations.
	
	<u>Treatment of hypertension in association with LVH</u>
	• Hypertensive patients with LVH should be treated with antihypertensive therapy to decrease the rate of subsequent cardiovascular events.
	• The choice of initial therapy can be influenced by the presence of LVH. Initial therapy can be drug treatment using ACE inhibitors, ARBs, long-acting CCBs, or thiazide/thiazide-like diuretics. Direct arterial vasodilators such as hydralazine or minoxidil should not be used.

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	Treatment of hypertension in association with nondiabetic chronic kidney disease • Individualize BP targets in patients with chronic kidney disease. Consider intensive targets (SBP <120 mmHg) in appropriate patients. • For patients with hypertension and proteinuric chronic kidney disease (urinary protein >150 mg per 24 hours or albumin to creatinine ratio >30 mg/mmol), initial therapy should be an ACE inhibitor or an ARB if there is intolerance to ACE inhibitors. • In most cases, combination therapy with other antihypertensive agents might be needed to reach target BP levels. • The combination of an ACE inhibitor and ARB is not recommended for patients with nonproteinuric chronic kidney disease. Treatment of hypertension in association with renovascular disease • Patients with hypertension attributable to atherosclerotic renal artery stenosis should be primarily medically managed because renal angioplasty and stenting offers no benefit over optimal medical therapy alone. • Renal artery angioplasty and stenting for atherosclerotic hemodynamically significant renal artery stenosis could be considered for patients with uncontrolled hypertension resistant to maximally tolerated pharmacotherapy, progressive renal function loss, and acute pulmonary edema. • Patients with confirmed renal fibromuscular dysplasia (FMD) should be referred to a hypertension specialist. • Renal artery angioplasty without stenting is recommended for treatment of FMD-related renal artery stenosis. Stenting is not recommended unless needed because of a periprocedural dissection. Surgical revascularization should be considered in cases of complex lesions less amendable to angioplasty, stenosis associated with complex aneurysm, and restenosis despite two unsuccessful attempts of angioplasty. Treatment of hypertension in association with diabetes mellitus • Persons with diabetes mellitus should be treated to attain SBP of <130 mmHg and DBP of <80 mmHg. • For persons with cardiovascular or kidney disease, including microalbuminuria, or with cardiovascular risk factors in addition to diabetes and hypertension, an ACE inhibitor or an ARB is recommended as initial therapy. • For persons with diabetes and hypertension not included in other guidelines in this section, appropriate choices include (in alphabetical order): ACE inhibitors, ARBs, dihydropyridine CCBs, and thiazide/thiazide-like diuretics. • If target BP levels are not achieved with standard-dose monotherapy, additional antihypertensive therapy should be used. For persons in whom combination therapy with an ACE inhibitor is being considered, a dihydropyridine CCB is preferable to a thiazide/thiazide-like diuretic. Resistant hypertension • Resistant hypertension is defined as BP above target despite three or more BP-lowering drugs at optimal doses preferably including a diuretic (and usually a renin-angiotensin-aldosterone system blocker and a CCB. • Accurate office and out-of-office BP measurement is essential. • Other reasons for apparent resistant hypertension should be eliminated before diagnosing true resistant hypertension, including nonadherence, white coat effect, and secondary hypertension. • Pharmacotherapy with the additional use of spironolactone, bisoprolol, doxazosin, amiloride, eplerenone, or clonidine with the baseline regimen decreases BP significantly, with the greatest BP-lowering shown with spironolactone.

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	• Patients with resistant hypertension should be referred to providers with expertise in diagnosis and management of hypertension. Hypertension and pediatrics • BP should be measured regularly in children three years of age or older; the auscultatory method is the gold-standard at present. • Initial therapy should be monotherapy, with an ACE inhibitor or ARB (not first-line in black children), or a long-acting dihydropyridine CCB. • The treatment t goal is systolic and diastolic office BP and/or ABPM < 95th percentile or <90th percentile in children with risk factors or target organ damage. • Complex cases should be referred to an expert in pediatric hypertension. Hypertension and pregnancy • Up to 7% of pregnancies are complicated by a hypertensive disorder of pregnancy, and approximately 5% of women will have chronic hypertension when they become pregnant. • The prevalence of hypertension in pregnancy is expected to increase with women becoming pregnant later in their reproductive years and the increasing prevalence of cardiovascular comorbidities such as increased preconception body mass index and maternal diabetes. • The possibility of pregnancy should be considered when managing women with hypertension who are of reproductive age. • Preconception counselling should be offered to all women with hypertension who are considering pregnancy. • ACE inhibitor and ARB therapy should be avoided before conception and during pregnancy unless there is a compelling indication for their use (i.e., proteinuric kidney disease). • Hypertension during pregnancy can increase the risk of adverse maternal and fetal outcomes, including an increased risk of preeclampsia, placental abruption, prematurity, small for gestational age infants, stillbirth, and maternal renal and retinal injury, thus generally requires involvement of an interdisciplinary team including obstetrical care providers. • Antihypertensive therapy is recommended for average SBP measurements of ≥140 mmHg or DBP measurements of ≥90 mmHg in pregnant women with chronic hypertension, gestational hypertension, or preeclampsia. Initial antihypertensive therapy should be monotherapy from the following first-line drugs: oral labetalol, oral methyldopa, long-acting oral nifedipine, or other oral b-blockers (acebutolol, metoprolol, pindolol, and propranolol). Other antihypertensive drugs can be considered as second-line drugs including: clonidine, hydralazine, and thiazide diuretics. • Women with severe hypertension with SBP ≥160 mmHg or DBP ≥110 mmHg in pregnancy or postpartum require urgent antihypertensive therapy because it is considered an obstetrical emergency. • Antihypertensive drugs used in breastfeeding women include: labetalol, methyldopa, long-acting nifedipine, enalapril, or captopril.
European Society of Hypertension: **2023 Guidelines for the management of arterial hypertension (2023)[10]**	General recommendations for antihypertensive drug treatment • BP lowering should be prioritized over the selection of specific antihypertensive drug classes because treatment benefit largely originates from BP reduction. • Five major drug classes including, ACE inhibitors, ARBs, β-blockers, CCBs, and Thiazide/Thiazide-like diuretics have effectively reduced blood pressure and cardiovascular events in randomized controlled trials. These drugs and their combinations are recommended as the basis of antihypertensive treatment strategies. • Initiation of therapy with a two-drug combination is recommended for most hypertensive patients. Preferred combinations should comprise a RAS blocker

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	(either an ACE inhibitor or an ARB) with a CCB or thiazide/thiazide-like diuretic. Other combinations of the five major drug classes can be used. • Initiation with monotherapy can be considered in patients with: grade 1 hypertension and low-risk if BP is only marginally elevated (less than 150 mmHg SBP and 95 mmHg DBP) high-normal BP and very high cardiovascular risk, frailty and/or and advance age. • If BP is not controlled with the initial two-drug combination by using the maximum recommended and tolerated dose of the respective components, treatment should be increased to a three-drug combination, usually a RAS blocker plus CCB plus thiazide/thiazide-like diuretic. • If BP is not controlled with a three-drug combination by using the maximum recommended and tolerated dose of the respective components, it is recommended to extend treatment according to the recommendations for resistant hypertension. • The use of single pill combinations should be preferred at any treatment step (i.e. during initiation of therapy with a two-drug combination and at any other step of treatment). • β-blocker should be used at initiation of therapy or at any treatment step as guideline-directed medical therapy (e.g., heart failure with reduced ejection fraction, anti-ischemic therapy in chronic coronary syndromes, heart rate control in atrial fibrillation). • β-blockers can be considered in the presence of several other conditions in which their use can be favorable. • The combination of two RAS blockers is not recommended due to increased risk of adverse events, in particular AKI. <u>True-resistant hypertension</u> • In resistant hypertension, it is recommended to reinforce lifestyle measures. • Drugs that can be considered as additional therapy in patients with resistant hypertension are preferably spironolactone (or other MRA), or β-blocker or Alpha-1 blockers or centrally acting agents (clonidine), or amiloride. • Thiazide/thiazide-like diuretics are recommended in resistant hypertension if estimated eGFR is ≥30 mL/min/1.73m^2. • Loop diuretics may be considered in patients with an estimated eGFR < 45 mL/min/1.73m^2 and should be used if eGFR falls below 30 mL/min/1.73m^2. • Chlorthalidone (12.5 to 25 mg once daily) could be used with or without a loop diuretic if eGFR is <30 mL/min/1.73m^2. • Renal deprivation can be considered as an additional treatment option in patients with resistant hypertension if eGFR is >40 mL/min/1.73m^2. • Patients with resistant hypertension should be followed very closely. Follow-up includes periodical ambulatory blood pressure monitoring and assessment of hypertension-mediated organ damage, particularly kidney function and serum potassium levels. Regular use of home blood pressure monitoring and monitoring of drug adherence are desirable.
National Institute for Health and Clinical Excellence: **Hypertension in adults: diagnosis and management (2019)**[11]	<u>Choosing antihypertensive drug treatment (for people with or without type II diabetes)</u> • Where possible, recommend treatment with drugs taken only once a day. • Prescribe non-proprietary drugs where these are appropriate and minimize cost. • Offer people with isolated systolic hypertension (systolic blood pressure ≥160 mmHg) the same treatment as people with both raised systolic and diastolic blood pressure. • Offer antihypertensive drug treatment to women of child-bearing potential with diagnosed hypertension in line with recommendations in this guideline. For women considering pregnancy or who are pregnant or breastfeeding, manage hypertension in line with the recommendations on Management of pregnancy with chronic hypertension and Breastfeeding in 'Hypertension in pregnancy'.

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	• When choosing antihypertensive drug treatment for adults of black African or African-Caribbean family origin, consider an angiotensin II receptor blocker, in preference to an angiotensin-converting enzyme inhibitor. Step one treatment • Patients <55 years of age should be offered a step one antihypertensive with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). • Offer an ACE inhibitor or an ARB to adults starting step 1 antihypertensive treatment who have type II diabetes and are of any age or family origin or those aged <55 years but not of black African or African-Caribbean family origin. • If an ACE inhibitor is not tolerated, offer an ARB. • Do not combine an ACE inhibitor with an ARB for the treatment of hypertension. • Offer a calcium channel blocker (CCB) to adults starting step 1 antihypertensive treatment who are >55 years of age and do not have diabetes and are of black African or African-Caribbean family origin and do not have type II diabetes and of any age. • If a CCB is not suitable, for example because of edema or intolerance, or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic. • If diuretic treatment is to be initiated or changed, offer a thiazide‑like diuretic, such as indapamide in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide. • For adults with hypertension who are already receiving treatment with bendroflumethiazide or hydrochlorothiazide, who have stable, well-controlled blood pressure, continue with their treatment. Step two treatment • Before considering next step treatment for hypertension discuss with the person if they are taking their medicine as prescribed and support adherence in line with NICE's guideline on "Medicines adherence: involving patients decisions about prescribed medicines and supporting adherence". • If hypertension is not controlled with a step one treatment of an ACE inhibitor or ARB, offer choice of one of the following drugs in addition to the step one treatment: a CCB or a thiazide-like diuretic. • If hypertension is not controlled in adults taking step one treatment of a CCB, offer the choice of one of the following drugs in addition to the step one treatment: an ACE inhibitor or an ARB or a thiazide-like diuretic. • If hypertension is not controlled in adults of black African or African–Caribbean family origin who do not have type 2 diabetes taking step one treatment, consider an ARB, in preference to an ACE inhibitor, in addition to step one treatment. Step three treatment • Before considering step three treatment, review the person's medications to ensure they are being taken at the optimal doses and discuss adherence (see recommendation under step two). • If hypertension is not controlled in adults taking step two treatment, offer a combination of an ACE inhibitor or ARB and a CCB and a thiazide-like diuretic. Step four treatment • If hypertension is not controlled in adults taking the optimal tolerated doses of an ACE inhibitor or an ARB plus a CCB and a thiazide-like diuretic, regard them as having resistant hypertension. • Before considering further treatment for a person with resistant hypertension, confirm elevated clinic blood pressure measurements using ambulatory or home

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	blood pressure recordings, assess for postural hypotension, and discuss adherence. • For people with confirmed resistant hypertension, consider adding a fourth antihypertensive drug as step four treatment or seeking specialist advice. • Consider further diuretic therapy with low-dose spironolactone for adults with resistant hypertension starting step four treatment who have a blood potassium level of 4.5 mmol/l or less. Use particular caution in people with a reduced estimated glomerular filtration rate because they have an increased risk of hyperkalemia. • When using further diuretic therapy for step four treatment of resistant hypertension, monitor blood sodium and potassium and renal function within one month of starting treatment and repeat as needed thereafter. • Consider an alpha-blocker or beta-blocker for adults with resistant hypertension starting step four treatment who have a blood potassium level of more than 4.5 mmol/l. • If blood pressure remains uncontrolled in people with resistant hypertension taking the optimal tolerated doses of four drugs, seek specialist advice.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in Blacks (2010)**[12]	• To attain and maintain blood pressure (BP) below target levels, multiple antihypertensive drugs will be required in most hypertensive blacks. • Use of two-drug combination therapy when SBP is >15 mm Hg and/or DBP is >10 mm Hg above goal levels is increasingly recommended as first-line therapy. • Two-drug regimens have generally contained a thiazide-type diuretic; however, the combination of a calcium channel blocker (CCB) with either an ACE inhibitor or an ARB has been shown equally efficacious in BP lowering but with demonstrated superiority (CCB+ACE) for hard clinical outcomes compared with the same ACE inhibitor plus a thiazide-type diuretic. • In secondary prevention patients, the combination therapy should include a drug(s) with the appropriate compelling indications. • Certain classes of antihypertensive medications, specifically diuretics and CCBs, lower BP on average more than β-blockers and renin-angiotensin system (RAS) blockers in black patients when used as monotherapies. • In the absence of compelling indications, when BP is near goal levels, monotherapy with a diuretic or a CCB is preferred. • Lifestyle modifications should be initiated in all patients with hypertension, whether or not pharmacotherapy is planned. • ACE inhibitors or ARBs are recommended as alternative monotherapy options in the treatment of hypertension in blacks. The rationale for their lower tier monotherapy recommendation is because they have consistently achieved lesser average reductions in BP relative to that observed with monotherapy using either a diuretic or CCB.
Kidney Disease Improving Clinical Outcomes Group: **KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease (2021)**[13]	<u>Blood pressure measurement</u> • The Work Group recommends standardized office blood pressure (BP) measurement in preference to routine office BP measurements for the management of high BP in adults. • The Work Group suggests that out-of-office BP measurements with ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM) be used to complement standardized office BP readings for the management of high BP. <u>Lifestyle interventions for lowering BP in patients with chronic kidney disease (CKD) not receiving dialysis</u> • The Work Group suggests targeting a sodium intake <2 grams of sodium per day (or <90 mmol of sodium per day, or <5 grams of sodium chloride per day) in patients with high BP and CKD. • The Work Group suggests that patients with high BP and CKD be advised to undertake moderate-intensity physical activity for a cumulative duration of at least

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	150 minutes per week, or to a level compatible with their cardiovascular and physical tolerance. <u>BP management in patients with CKD, with or without diabetes, not receiving dialysis</u> • The Work Group suggests that adults with high BP and CKD be treated with a target systolic BP (SBP) of <120 mmHg, when tolerated, using standardized office BP measurement. • The Work Group recommends starting renin-angiotensin-system inhibitors (RASi) (angiotensin-converting enzyme inhibitor [ACEi] or angiotensin II receptor blocker [ARB]) for people with high BP, CKD, and severely increased albuminuria without diabetes. • The Work Group suggests starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately increased albuminuria without diabetes. • The Work Group recommends starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately-to-severely increased albuminuria with diabetes. • The Work Group recommends avoiding any combination of ACEi, ARB, and direct renin inhibitor (DRI) therapy in patients with CKD, with or without diabetes. <u>BP management in kidney transplant recipients</u> • Treat adult kidney transplant recipients with high BP to a target BP of <130 mmHg systolic and <80 mmHg diastolic using standardized office BP measurement. • The Work Group recommends that a dihydropyridine calcium channel blocker (CCB) or an ARB be used as the first-line antihypertensive agent in adult kidney transplant recipients. <u>BP management in children with CKD</u> • The Work Group suggests that in children with CKD, 24-hour mean arterial pressure by ABPM should be lowered to <50th percentile for age, sex, and height.
American College of Cardiology/ American Heart Association Task Force: **Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults (2017)[14]**	<u>Initiation of Blood Pressure (BP) Treatment for Overall Cardiovascular Disease (CVD) Risk</u> • Use of BP-lowering medications is recommended for secondary prevention of recurrent CVD events in patients with clinical CVD and an average systolic blood pressure (SBP) ≥130 mmHg or an average diastolic blood pressure (DBP) of ≥80 mmHg and for primary prevention in adults with an estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk of ≥10% and an average SBP of ≥130 mmHg or an average ≥80 mmHg. • Use of BP-lowering medication is recommended for primary prevention of CVD in adults with no history of CVD and with an estimated 10-year ASCVD risk <10% and an SBP of ≥140 mmHg or a DBP of ≥90 mmHg. • Simultaneous use of an angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), and/or renin inhibitor is potentially harmful and is not recommended to treat adults with hypertension. • For adults with confirmed hypertension and known CVD or 10-year ASCVD risk of ≥10%, a BP target <130/80 mmHg is recommended. For adults with confirmed hypertension without additional markers of increased CVD risk, a BP target <130/80 mmHg may be reasonable. • For initiation of antihypertensive drug therapy, first-line agents include thiazide diuretics, calcium channel blockers (CCBs), and ACE inhibitors or ARBs. • Initiation of antihypertensive drug therapy with two first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended in adults with stage 2 hypertension and an average BP >20/10 mmHg above their BP target. • Initiation of antihypertensive drug therapy with a single antihypertensive drug is

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	reasonable in adults with stage 1 hypertension and BP goal <130/80 mmHg with dosage titration and sequential addition of other agents to achieve the BP target. Stable Ischemic Heart Disease (SIHD) • In adults with SIHD and hypertension, a BP target <130/80 is recommended. • Adults with SIHD and hypertension (BP ≥130/80 mmHg) should be treated with medications [e.g., guideline-directed medical therapy (GDMT) beta-blockers, ACE inhibitors, or ARBs] for compelling indications [e.g., previous myocardial infarction (MI), stable angina] as first-line therapy, with the addition of other drugs (e.g., dihydropyridine CCBs, thiazide diuretics, and/or mineralocorticoid receptor antagonists) as needed to further control hypertension. • In adults with SIHD with angina and persistent uncontrolled hypertension, the addition of dihydropyridine CCBs to GDMT beta-blockers is recommended. • In adults who have had a MI or acute coronary syndrome, it is reasonable to continue GDMT beta-blockers beyond three years as long-term therapy for hypertension. • Beta-blockers and/or CCBs might be considered to control hypertension in patients with coronary artery disease (CAD) had an MI more than three years ago and have angina. Heart Failure • In adults with increased risk of HF, the optimal BP in those with hypertension should be <130 mmHg. • Adults with HFrEF and hypertension should be prescribed GDMT titrated to attain a BP <130/80 mmHg. • Non-dihydropyridine CCBs are not recommended in the treatment of hypertension in adults with HFrEF. • In adults with HFpEF who present with symptoms of volume overload, diuretics should be prescribed to control hypertension. • Adults with HFpEF and persistent hypertension after management of volume overload should be prescribed ACE inhibitors or ARBs and beta-blockers titrated to attain SBP <130 mmHg. CKD • Adults with hypertension and CKD should be treated to a BP goal <130/80 mmHg. • In adults with hypertension and CKD [stage 3 or higher or stage 1 or 2 with albuminuria (≥300 mg/d, or ≥300 mg/g albumin-to-creatinine ratio or the equivalent in the first morning void)], treatment with an ACE inhibitor is reasonable to slow kidney disease progression. Treatment with an ARB may be reasonable if an ACE inhibitor is not tolerated. • After kidney transplantation, it is reasonable to treat patients with hypertension to a BP goal <130/80 mmHg and with a CCB on the basis of improved glomerular filtration rate (GFR) and kidney survival. Cerebrovascular Disease • In adults with intracerebral hemorrhage (ICH) who present with SBP >220 mmHg, it is reasonable to use continuous intravenous (IV) drug infusion and close BP monitoring to lower levels. Immediate lowering of SBP to <140 mmHg in adults with spontaneous ICH who present within six hours of the acute event and have an SBP between 150 mmHg and 220 mmHg is not of benefit to reduce death or severe disability and can be potentially harmful. • Adults with acute ischemic stroke and elevated BP who are eligible for treatment with IV tissue plasminogen activator (tPA) should have their BP slowly lowered to <185/110 mmHg before thrombolytic therapy is initiated. • In adults with an acute ischemic stroke, BP should be <185/110 mmHg before

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	administration of IV tPA and should be maintained below 180/105 mmHg for at least the first 24 hours after initiation drug therapy. • Starting or restarting antihypertensive therapy during hospitalization in patients with BP >140/90 mmHg who are neurologically stable is safe and reasonable to improve long-term BP control, unless contraindicated. • In patient with BP ≥220/120 mmHg who did not receive IV alteplase or endovascular treatment and have no comorbid conditions requiring acute antihypertensive treatment, the benefit of initiating or reinitiating treatment of hypertension within the first 48 to 72 hours is uncertain. It might be reasonable to lower BP by 15% during the first 24 hours after onset of stroke. In patients with BP <220/120 mmHg with the same conditions, initiating or reinitiating treatment of hypertension within the first 48 to 72 hours after an acute ischemic stroke is not effective to prevent death or dependency. • Adults with previously treated stroke or transient ischemic attack should be restarted on antihypertensive treatment after the first few days of the index event to reduce the risk of recurrent stroke and other vascular events. Treatment with a thiazide diuretic, ACE inhibitor, or ARB, or combination treatment consisting of a thiazide diuretic plus ACE inhibitor, is useful. • Adults not previously treated for hypertension who experienced a stroke or transient ischemic attack and have an established BP ≥140/90 mmHg should be prescribed antihypertensive treatment a few days after the index event to reduce the risk of recurrent stroke and other vascular event. • For adults who experience a stroke or transient ischemic attack, selection of specific drugs should be individualized on the basis of patient comorbidities and agent pharmacological class. • For adults who experience a stroke or transient ischemic attack, a BP goal <130/80 mmHg may be reasonable. • For adults with a lacunar stroke, a target SBP goal <130 mmHg may be reasonable. • In adults previously untreated for hypertension who experience an ischemic stroke or transient ischemic attack and have an SBP <140 mmHg and a DBP <90 mmHg, the usefulness of initiating antihypertensive treatment is not well established. <u>Peripheral Artery Disease (PAD)</u> • Adults with hypertension and PAD should be treated similarly to patients with hypertension without PAD. <u>Diabetes Mellitus (DM)</u> • In adults with DM and hypertension, antihypertensive drug treatment should be initiated at a BP of ≥130/80 mmHg with a treatment goal <130/80 mmHg. • In adults with DM and hypertension, all first-line classes of antihypertensive agents (i.e., diuretics, ACE inhibitors, ARBs, and CCBs) are useful and effective. • In adults with DM and hypertension, ACE inhibitors or ARBs may be considered in the presence of albuminuria. <u>Atrial Fibrillation, Valvular Heart Disease, and Aortic disease</u> • Treatment of hypertension can be useful for prevention of recurrence of AF. • In adults with asymptomatic aortic stenosis, hypertension should be treated with pharmacotherapy, starting at a low dose and gradually titrating upward as needed. • In patients with chronic aortic insufficiency, treatment of systolic hypertension with agents that do not slow the heart rate (i.e., avoid beta-blockers) is reasonable. • Beta-blockers are recommended as the preferred antihypertensive agents in patients with hypertension and thoracic aortic disease. <u>Racial and Ethnic Differences in Treatment</u>

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	• In black adults with hypertension but without HF or CKD, including those with DM, initial antihypertensive treatment should include a thiazide-type diuretic or CCB. Two or more antihypertensive medications are recommended to achieve a BP target <130/80 mmHg in most adults with hypertension, especially in black adults with hypertension. Pregnancy • Women with hypertension who become pregnant, or are planning to become pregnant, should be transitioned to methyldopa, nifedipine, and/or labetalol during pregnancy. • Women with hypertension who become pregnant should not be treated with ACE inhibitors, ARBs, or direct renin inhibitors. Older Persons • Treatment of hypertension with an SBP treatment goal <130 mmHg is recommended for noninstitutionalized ambulatory community-dwelling adults (≥65 years of age) with an average SBP of ≥130 mmHg. • For older adults (≥65 years of age) with hypertension and a higher burden of comorbidity and limited life expectancy, clinical judgment, patient preference, and a team-based approach to assess risk/benefit is reasonable for decisions regarding intensity of BP lowering and choice of antihypertensive drugs. Hypertensive Crises • In adults with a hypertensive emergency, admission to an intensive care unit is recommended for continuous monitoring of BP and target organ damage and for parenteral administration of an appropriate agent. • For adults with a compelling condition (i.e., aortic dissection, severe pre-eclampsia or eclampsia, or pheochromocytoma crisis), SBP should be reduced to <140 mmHg during the first hour and to <120 mmHg in aortic dissection. • For adults without a compelling condition, SBP should be reduced by no more than 25% within the first hours; then, if stable, to 160/100 mmHg within the next two to six hours; and then cautiously to normal during the following 24 to 48 hours. Cognitive Decline and Dementia • In adults with hypertension, BP lowering is reasonable to prevent cognitive decline and dementia. Patients Undergoing Surgical Procedures • In patients with hypertension undergoing major surgery who have been on beta-blockers chronically, beta-blockers should be continued. • In patients with hypertension undergoing planned elective major surgery, it is reasonable to continue medical therapy for hypertension until surgery. • In patients with hypertension undergoing major surgery, discontinuation of ACE inhibitors or ARBs perioperatively may be considered. • In patients with planned elective major surgery and SBP ≥180 mmHg or DBP ≥110 mmHg, deferring surgery may be considered. • For patients undergoing surgery, abrupt pre-operative discontinuation of beta-blockers or clonidine is potentially harmful. • Beta-blockers should not be started on the day of surgery in beta-blocker-naïve patients. • Patients with intraoperative hypertension should be managed with IV medications until such time as oral medications can be resumed.
American Diabetes Association:	Hypertension/blood pressure control • Blood pressure should be measured at every routine visit. When possible, patients

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Standards of Medical Care in Diabetes (2023)[15]	found to have elevated blood pressure (systolic blood pressure 120 to 129 mmHg and diastolic <80 mmHg) should have blood pressure confirmed using multiple readings, including measurements on a separate day, to diagnose hypertension. Patients with blood pressure ≥180/110 and cardiovascular disease could be diagnosed with hypertension at a single visit. • All hypertensive patients with diabetes should monitor their blood pressure at home. • For patients with diabetes and hypertension, blood pressure targets should be individualized through a shared decision-making process that addresses cardiovascular risk, potential adverse effects of antihypertensive medications, and patient preferences. • Individuals with diabetes and hypertension qualify for antihypertensive drug therapy when the blood pressure is persistently elevated ≥130/80 mmHg. The on-treatment target blood pressure goal is <130/80 mmHg, if it can be safely attained. • In pregnant patients with diabetes and preexisting hypertension, a blood pressure target of 110 to 135/85 is suggested in the interest of reducing the risk for accelerated maternal hypertension and minimizing impaired fetal growth. • For patients with blood pressure >120/80, lifestyle intervention consists of weight loss when indicated, a Dietary Approaches to Stop Hypertension (DASH)-style eating pattern including reducing sodium and increasing potassium intake, moderation of alcohol intake, and increased physical activity. • Patients with confirmed office-based blood pressure ≥130/80 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of pharmacologic therapy to achieve blood pressure goals. • Patients with confirmed office-based blood pressure ≥160/100 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of two drugs or a single pill combination of drugs demonstrated to reduce cardiovascular events in patients with diabetes. • Treatment for hypertension should include drug classes demonstrated to reduce cardiovascular events in patients with diabetes (ACE inhibitors, angiotensin receptor blockers, thiazide-like diuretics, or dihydropyridine calcium channel blockers). ACE inhibitors or angiotensin receptor blockers are recommended first-line therapy for hypertension in people with diabetes and coronary artery disease. • Multiple-drug therapy is generally required to achieve blood pressure targets (but not a combination of ACE inhibitors and angiotensin receptor blockers). • An ACE inhibitor or angiotensin receptor blocker, at the maximum tolerated dose indicated for blood pressure treatment, is the recommended first-line treatment for hypertension in patients with diabetes and urinary albumin–to–creatinine ratio ≥300 mg/g creatinine or 30 to 299 mg/g creatinine. If one class is not tolerated, the other should be substituted. • For patients treated with an ACE inhibitor, angiotensin receptor blocker, or diuretic, serum creatinine/estimated glomerular filtration rate and serum potassium levels should be monitored at least annually. • Patients with hypertension who are not meeting blood pressure targets on three classes of antihypertensive medications (including a diuretic) should be considered for mineralocorticoid receptor antagonist therapy. <u>Chronic kidney disease</u> • At least once a year, assess urinary albumin (e.g., spot urinary albumin–to–creatinine ratio) and estimated glomerular filtration rate in patients with type 1 diabetes with duration of five or more years and in all patients with type 2 diabetes. • In people with established diabetic kidney disease, urinary albumin (e.g., spot urinary albumin-to-creatinine ratio) and estimated glomerular filtration rate should be monitored one to four times per year depending on the stage of the disease.

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	Optimize glucose control to reduce the risk or slow the progression of chronic kidney disease (CKD). • For patients with type 2 diabetes and diabetic kidney disease, use of a sodium-glucose cotransporter 2 inhibitor in patients with an estimated glomerular filtration rate ≥20 mL/min/1.73 m^2 and urinary albumin ≥200 mg/g creatinine is recommended to reduce CKD progression and cardiovascular events. • For patients with type 2 diabetes and diabetic kidney disease, use of a sodium–glucose cotransporter 2 inhibitor is recommended to reduce chronic kidney disease progression and cardiovascular events in patients with an estimated glomerular filtration rate ≥20 mL/min/1.73 m^2 and urinary albumin ranging from normal to 200 mg/g creatinine. • In people with type 2 diabetes and diabetic kidney disease, consider use of sodium–glucose cotransporter 2 inhibitors (if estimated glomerular filtration rate is ≥20 mL/min/1.73 m^2), a glucagon-like peptide 1 agonist, or a nonsteroidal mineralocorticoid receptor antagonist (if estimated glomerular filtration rate is ≥25 mL/min/1.73 m^2) additionally for cardiovascular risk reduction. • In people with chronic kidney disease and albuminuria who are at increased risk for cardiovascular events or chronic kidney disease progression, a nonsteroidal mineralocorticoid receptor antagonist shown to be effective in clinical trials is recommended to reduce chronic kidney disease progression and cardiovascular events. • Optimize blood pressure control and reduce blood pressure variability to reduce the risk or slow the progression of CKD. • Do not discontinue renin-angiotensin system blockade for minor increases in serum creatinine (≤30%) in the absence of volume depletion. • For people with nondialysis-dependent stage 3 or higher CKD, dietary protein intake should be a maximum of 0.8 g/kg body weight per day (the recommended daily allowance). For patients on dialysis, higher levels of dietary protein intake should be considered, since protein energy wasting is a major problem in some dialysis patients. • In nonpregnant patients with diabetes and hypertension, either an ACE inhibitor or an angiotensin receptor blocker is recommended for those with modestly elevated urinary albumin–to–creatinine ratio (30 to 299 mg/g creatinine) and is strongly recommended for those with urinary albumin–to–creatinine ratio ≥300 mg/g creatinine and/or estimated glomerular filtration rate <60 mL/min/1.73 m^2. • Periodically monitor serum creatinine and potassium levels for the development of increased creatinine and hyperkalemia when ACE inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists are used, or hypokalemia when diuretics are used. • An ACE inhibitor or an angiotensin receptor blocker is not recommended for the primary prevention of CKD in patients with diabetes who have normal blood pressure, normal urinary albumin–to–creatinine ratio (<30 mg/g creatinine), and normal estimated glomerular filtration rate. • Patients should be referred for evaluation by a nephrologist if they have continuously increasing urinary albumin levels and/or continuously decreasing estimated glomerular filtration rate and an estimated glomerular filtration rate <30 mL/min/1.73 m^2. • Promptly refer to a nephrologist for uncertainty about the etiology of kidney disease, difficult management issues, and rapidly progressing kidney disease.
American Association for the Study of Liver Diseases: **Diagnosis,**	<u>Treatment of ascites</u> • Moderate sodium restriction (2 g or 90 mmol/day) and diuretics (spironolactone with or without furosemide) are the first-line treatment in patients with cirrhosis and grade 2 ascites. • After ascites is adequately mobilized, attempts should be made to taper the

Clinical Guideline	Recommendation(s)
Evaluation, and Management of Ascites, Spontaneous Bacterial Peritonitis and Hepatorenal Syndrome: 2021 Practice Guidance (2021)[16]	diuretics to the lowest dose necessary to maintain minimal or no ascites to prevent the development of adverse effects. • Fluid restriction is not necessary unless serum sodium is <125 mmol/L. • In patients receiving diuretics, body weight and serum creatinine and sodium should be regularly monitored to assess response and to detect the development of adverse effects. • Human albumin solution (20 to 40 g/week) or baclofen administration (10 mg/day, with a weekly increase of 10 mg/day, up to 30 mg/day) can be considered in cases of severe muscle cramps. • Large-volume paracentesis is the first-line treatment of grade 3 ascites. After paracentesis, sodium restriction and diuretics should be started. • Referral for liver transplant evaluation should be considered in patients with grade 2 or 3 ascites. • Nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers should be avoided in patients with cirrhosis and ascites. • Aminoglycosides should be avoided whenever possible in the treatment of bacterial infections. • For patients with cirrhosis and diuretic-responsive ascites, controversial data suggest potential benefits of long-term infusion of human albumin solution. At present, no recommendation can be made for its use in routine clinical practice.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the thiazide-like diuretics are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Thiazide-Like Diuretics[1-3]

Indication	Chlorthalidone*	Indapamide	Metolazone
Edema			
Adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, and corticosteroid and estrogen therapy	✔		
Treatment of salt and fluid retention associated with congestive heart failure		✔	
Treatment of salt and water retention, including edema accompanying congestive heart failure			✔
Treatment of salt and water retention, including edema accompanying renal disease, including the nephrotic syndrome and states of diminished renal function			✔
Hypertension			
Treatment of hypertension	✔ †	✔ †	✔ †

*Chlorthalidone is also useful in the treatment of edema due to various forms of renal dysfunction such as nephrotic syndrome, acute glomerulonephritis, and chronic renal failure.
†Alone or in combination with other antihypertensive agents.

IV. Pharmacokinetics

The pharmacokinetic parameters of the thiazide-like diuretics are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Thiazide-Like Diuretics[4]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Chlorthalidone	65	75	Not reported	Renal (50 to 74)	40 to 60
Indapamide	100	71 to 79	Liver, extensive (% not reported)	Bile (23) Feces (16 to 20) Renal (60 to 70)	14 to 15
Metolazone	40 to 65	Not reported	Not reported	Renal (56)	8 to 14

V. Drug Interactions

Major drug interactions with the thiazide-like diuretics are listed in Table 5.

Table 5. Major Drug Interactions with the Thiazide-Like Diuretics[4]

Generic Name(s)	Interaction	Mechanism
Thiazide-like diuretics (chlorthalidone, indapamide, metolazone)	Dofetilide	Increased potassium excretion caused by thiazide diuretic administration Hypokalemia may occur.
Thiazide-like diuretics (chlorthalidone, indapamide, metolazone)	Lithium	Thiazide-like diuretics may decrease the renal excretion of lithium and produce elevated serum lithium concentrations with toxicity.
Thiazide-like diuretics (chlorthalidone, indapamide, metolazone)	Digitalis glycosides	Excretion of potassium and magnesium is increased by thiazide-like diuretics. Potassium and magnesium depletion can sensitize the myocardium to the toxic effects of digitalis glycosides.
Thiazide-like diuretics (chlorthalidone, indapamide, metolazone)	Loop diuretics (Bumetanide, ethacrynic acid, furosemide, torsemide)	Both groups have synergistic effects that may result in profound diuresis and serious electrolyte abnormalities
Thiazide-like diuretics (chlorthalidone, indapamide, metolazone)	NSAIDs	Concurrent use of NSAIDs and thiazide-like diuretics may result in reduced diuretic effectiveness and possible nephrotoxicity.
Thiazide-like diuretics (chlorthalidone, metolazone)	Bepridil	Concurrent use of thiazide-like diuretics and bepridil may result in hypokalemia and subsequent cardiotoxicity (torsades de pointes).
Thiazide-like diuretics (chlorthalidone, metolazone)	Flecainide	Concurrent use of thiazide-like diuretics and flecainide may result in increased risk of electrolyte imbalance and subsequent cardiotoxicity.

NSAIDs=nonsteroidal anti-inflammatory drugs

VI. Adverse Drug Events

The most common adverse drug events reported with the thiazide-like diuretics are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Thiazide-Like Diuretics[1-4]

Adverse Event(s)	Chlorthalidone	Indapamide	Metolazone
Cardiovascular			
Chest pain	-	<5	✔
Irregular heartbeat	-	<5	-
Orthostatic hypotension	✔	<5	✔
Palpitations	-	<5	✔
Peripheral edema	-	<5	-
Premature ventricular contractions	-	<5	-
Venous thrombosis	-	-	✔

Adverse Event(s)	Chlorthalidone	Indapamide	Metolazone
Volume depletion	-	-	✔
Central Nervous System			
Anxiety	-	≥5	-
Blurred vision	-	<5	✔
Depression	-	<5	-
Dizziness	✔	≥5	✔
Drowsiness	-	<5	✔
Fatigue	-	≥5	✔
Headache	✔	≥5	✔
Insomnia	-	<5	-
Lethargy	-	≥5	-
Lightheadedness	-	<5	✔
Nervousness	-	<5	-
Neuropathy	-	-	✔
Paresthesia	✔	<5	✔
Restlessness	✔	-	✔
Syncope	-	-	✔
Tension	-	≥5	-
Vertigo	✔	<5	✔
Weakness	✔	≥5	✔
Xanthopsia	✔	-	-
Dermatological			
Dermatitis	-	-	✔
Petechiae	-	-	✔
Photosensitivity	✔	-	✔
Pruritus	-	<5	✔
Purpura	✔	-	✔
Rash	✔	<5	✔
Skin necrosis	-	-	✔
Stevens-Johnson syndrome	-	-	✔
Toxic epidermal necrolysis	✔	✔	✔
Urticaria	✔	<5	✔
Gastrointestinal			
Abdominal pain	-	<5	✔
Anorexia	✔	<5	✔
Constipation	✔	<5	✔
Cramping	✔	-	-
Diarrhea	✔	<5	✔
Dry mouth	-	<5	✔
Dyspepsia	-	<5	-
Epigastric distress	-	-	✔
Gastric irritation	✔	<5	-
Nausea	✔	<5	✔
Pancreatitis	✔	-	✔
Vomiting	✔	<5	✔
Genitourinary			
Impotence	✔	<5	✔
Nocturia	-	<5	✔
Polyuria	-	<5	-
Hematologic			
Agranulocytosis	✔	-	✔
Aplastic anemia	✔	-	✔
Leukopenia	✔	-	✔
Thrombocytopenia	✔	-	✔

Adverse Event(s)	Chlorthalidone	Indapamide	Metolazone
Laboratory Test Abnormalities			
Blood urea nitrogen increased	-	<5	✔
Hypercalcemia	✔	✔	✔
Hyperglycemia	✔	<5	✔
Hyperlipidemia	✔	-	-
Hyperuricemia	✔	<5	✔
Hypochloremia	-	<5	✔
Hypokalemia	✔	3 to 7	✔
Hypomagnesemia	✔	✔	✔
Hyponatremia	✔	<5	-
Hypophosphatemia	-	-	✔
Serum creatinine increased	-	-	✔
Musculoskeletal			
Asthenia	-	<5	-
Back pain	-	≥5	-
Joint pain	-	-	✔
Hypertonia	-	<5	-
Muscle spasm	✔	≥5	✔
Renal			
Glycosuria	✔	<5	✔
Respiratory			
Cough	-	<5	-
Pharyngitis	-	<5	-
Rhinitis	-	≥5	-
Sinusitis	-	<5	-
Other			
Chills	-	-	✔
Conjunctivitis	-	<5	-
Gout	-	-	✔
Hemoconcentration	-	-	✔
Hepatitis	-	-	✔
Infection	-	≥5	-
Jaundice	✔	-	✔
Necrotizing angiitis/vasculitis	-	-	✔
Vasculitis	✔	<5	-
Weight loss	-	<5	-

✔ Percent not specified
- Event not reported

VII. Dosing and Administration

The usual dosing regimens for the thiazide-like diuretics are listed in Table 7.

Table 7. Usual Dosing Regimens for the Thiazide-Like Diuretics[1-4]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Chlorthalidone	Edema: Tablet: initial, 50 to 100 mg/day or 100 mg on alternate days; maintenance, 90 to 120 mg on alternate days or 120 mg/day Hypertension: Tablet: initial, 12.5 to 25 mg/day; maintenance, 25 to 100 mg/day	Safety and efficacy in children have not been established.	Tablet: 15 mg 25 mg 50 mg

Indapamide	Edema: Tablet: initial, 2.5 mg/day; maintenance, 2.5 to 5 mg/day Hypertension: Tablet: initial, 1.25 mg/day; maintenance, 2.5 to 5 mg/day	Safety and efficacy in children have not been established.	Tablet: 1.25 mg 2.5 mg
Metolazone	Edema: Tablet: 5 to 20 mg/day Hypertension: Tablet: initial, 2.5 to 5 mg/day; maintenance, 5 to 20 mg/day	Safety and efficacy in children have not been established.	Tablet: 2.5 mg 5 mg 10 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the thiazide-like diuretics are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Thiazide-Like Diuretics

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
SHEP Cooperative Research Group[17]and Kostis et al.[18] (1991 and 1995) SHEP Chlorthalidone 12.5 mg QD vs placebo Dosage was doubled for patients failing to achieve SBP goals. If SBP goal was not reached with chlorthalidone 25 mg QD, atenolol 25 mg QD or matching placebo was added to the drug regimen. Reserpine 0.05 mg QD or matching placebo was substituted in patients with contraindications	DB, MC, PC, RCT Patients aged ≥60 years with SBP between 160 and 219 mm Hg and DBP <90 mm Hg	N=4,736 Mean 4.5 years	Primary: Total stroke Secondary: Sudden or rapid cardiac death (defined as death within 1 hour or within 1 to 24 hours of the onset of severe cardiac symptoms), nonfatal or fatal MI, other cardiovascular death, TIA	Primary: With a mean follow-up of 4.5 years, the stroke occurred in 103 patients in the active treatment group compared to 159 patients in the placebo group (RR, 0.64; 95% CI, 0.5 to 0.82; P=0.0003). Stroke incidence was lower in patients taking active treatment compared to placebo in all baseline age groups: 60 to 69 years (34 vs 47 events, respectively), 70 to 79 years (48 vs 74 events, respectively), 80+ years (21 vs 38 events, respectively). The results were stratified according to whether patients had had previous antihypertensive therapy or not. In both stratified groups, there was a decrease in the risk of stroke with active treatment compared to placebo. For patients who were not receiving antihypertensive medication at initial contact, the RR, of stroke was 0.69 (95% CI, 0.51 to 0.95; P=0.02). For patients who had been receiving antihypertensive medication at initial contact, the RR, of stroke was 0.57 (95% CI, 0.38 to 0.85; P=0.01). Secondary: There were 23 sudden and 21 rapid deaths in the active treatment group compared to 23 sudden and 24 rapid deaths in the placebo group (RR, 10; 95% CI, 0.56 to 1.78 vs RR, 0.87; 95% CI, 0.48 to 1.56, respectively). There were 50 nonfatal and 15 fatal MIs in the active treatment group compared to 74 nonfatal and 26 fatal MIs in the placebo group (RR, 0.67; 95% CI, 0.47 to 0.96 vs RR, 0.57; 95% CI, 0.30 to 18, respectively. There were 21 other cardiovascular deaths in the active treatment group compared to 25 in the placebo group (RR, 0.87; 95% CI, 0.49 to 1.55). There were 62 TIAs in the active treatment group compared to 82 in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
to atenolol.				placebo group (RR, 0.75; 95% CI, 0.54 to 14). In the combined endpoints, the RR, of nonfatal MI or coronary heart disease death was 0.73 (95% CI, 0.57 to 0.94), CHD was 0.75 (95% CI, 0.60 to 0.94), cardiovascular disease was 0.68 (95% CI, 0.58 to 0.79). The RR, for atenolol were 0.84 (95% CI, 0.54 to 1.30) for death, 1.34 (95% CI, 0.80 to 2.28) for stroke, and 17 (95% CI, 0.71 to 1.61) for cardiovascular disease. The RR, for reserpine were 0.65 (95% CI, 0.26 to 1.59) for death, 0.27 (95% CI, 0.04 to 2.26) for stroke, and 0.55 (95% CI, 0.20 to 1.49) for cardiovascular disease.
ALLHAT Collaborative Research Group[19] (2000) ALLHAT Chlorthalidone 12.5 to 25 mg QD vs doxazosin 2 to 8 mg QD	AC, DB, MC, RCT Patients aged 55 years or older who had stage 1 or stage 2 HTN with ≥1 additional risk factor for CHD events (including previous MI or stroke >6 months ago, left ventricular hypertrophy or echocardiography, history of type 2 diabetes, current cigarette smoking, high density lipoprotein cholesterol <35 mg/dL, or documentation of other atherosclerotic cardiovascular	N=24,335 Median 3.3 years	Primary: Fatal CHD or nonfatal MI combined Secondary: All cause mortality, fatal and nonfatal stroke, combined CHD, combined cardiovascular disease, cancer, end-stage renal disease	Primary: There was no significant difference in the primary outcome between doxazosin and chlorthalidone treatments (risk ratio, 13; 95% CI, 0.90 to 1.17; P=0.71). Secondary: Total mortality did not differ between the doxazosin and chlorthalidone treatments (four year rates, 9.62 and 9.08%, respectively; RR, 13; 95% CI, 0.90 to 1.15; P=0.56). The doxazosin group, compared with the chlorthalidone group, had a higher risk of stroke (RR 1.19; 95% CI, 11 to 1.40; P=0.04) and combined cardiovascular disease (four year rates 25.45 vs 21.76%; RR, 1.25; 95% CI, 1.17 to 1.33; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	disease)			
Black et al.[20] (2008) ALLHAT Chlorthalidone 12.5 to 25 mg QD vs amlodipine 2.5 to 10 mg QD vs lisinopril 10 to 40 mg QD	MC, RCT Men and women, age 55 years old and older, with HTN and metabolic syndrome	N=17,515 4.9 years (mean)	Primary: Fatal coronary heart disease and nonfatal MI Secondary: All cause mortality, fatal and nonfatal stroke, combined coronary heart disease, combined cardiovascular disease	Primary: For patients with metabolic syndrome, there was no significant difference in rates of coronary heart disease and nonfatal MI with amlodipine vs chlorthalidone (RR, 0.96; 95% CI, 0.79 to 1.16), or lisinopril vs chlorthalidone (RR, 15; 95% CI, 0.88 to 1.27). Secondary: For patients with metabolic syndrome, there were no significant differences found between amlodipine vs chlorthalidone in all secondary endpoints (P value not significant). For patients without metabolic syndrome, amlodipine treatment was associated with significantly more heart failure, but in patients with metabolic syndrome, there was no difference (P=0.03). Patients with metabolic syndrome who received lisinopril experienced more heart failure and cardiovascular disease than those who received chlorthalidone (RR, 1.31; 95% CI, 14 to 1.64 and RR, 1.19; 95% CI, 17 to 1.32).
ALLHAT Collaborative Research Group[21] (2002) ALLHAT Chlorthalidone 12.5 to 25 mg/day vs amlodipine 2.5 to 10 mg/day vs lisinopril 10 to 40	DB, MC, RCT Patients ≥55 years with HTN and ≥1 additional CHD risk factor	N=33,357 4.9 years (mean)	Primary: Combined fatal CHD or nonfatal MI Secondary: All-cause mortality, fatal and nonfatal stroke, combined CHD, combined cardiovascular disease (combined CHD, stroke, treated angina without hospitalization,	Primary: There were no significant differences in the primary outcome between lisinopril (11.4%), amlodipine (11.3%), and chlorthalidone (11.5%). Secondary: All-cause mortality did not differ between groups. Five year SBPs were significantly higher in the lisinopril (2 mm Hg; P<0.001) and amlodipine groups (0.8 mm Hg; P=0.03) compared to chlorthalidone, and five year DBPs were significantly lower with amlodipine (0.8 mm Hg; P<0.001). Amlodipine had a higher six year rate of heart failure compared to chlorthalidone (10.2 vs 7.7%; RR, 1.38; 95% CI, 1.25 to 1.52). Lisinopril had a higher six year rate of combined cardiovascular disease (33.3 vs 30.9%; RR, 1.10; 95% CI, 15 to 1.16); stroke (6.3 vs 5.6%; RR,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day			heart failure, and PAD)	1.15; 95% CI, 12 to 1.30) and heart failure (8.7 vs 7.7%; RR, 1.19; 95% CI, 17 to 1.31).
Rahman et al.[22] (2012) ALLHAT Chlorthalidone 12.5 to 25 mg/day vs amlodipine 2.5 to 10 mg/day vs lisinopril 10 to 40 mg/day	Long-term, post-trial, follow-up Patients in ALLHAT stratified based on eGFR	N=31,350 4 to 8 years	Primary: Cardiovascular mortality Secondary: Total mortality, CHD, cardiovascular disease, stroke, heart failure, ESRD	Primary: After an average of 8.8 years of follow-up, total mortality was significantly higher in patients with moderate/severe eGFR reduction (eGFR <60 mL/min/1.73 m^2) compared to patients with normal/increased (eGFR ≥90 mL/min/1.73 m^2) and mildly reduced eGFR (eGFR 60 to 89 mL/min/1.73 m^2) (P<0.001). In patients with moderate/severe eGFR reduction, there was no significant difference in cardiovascular mortality between chlorthalidone and amlodipine (P=0.64), or chlorthalidone and lisinopril (P=0.56). Secondary: No significant differences were observed for any of the secondary endpoints among eGFR reduction groups.
Muntner et al.[23] (2014) ALLHAT Chlorthalidone 12.5 to 25 mg/day vs amlodipine 2.5 to 10 mg/day vs lisinopril 10 to 40 mg/day	Post-hoc analysis of ALLHAT Patients in ALLHAT with 5, 6, or 7 visits in 6 to 28 months of follow-up	N=24,004 6 to 28 months	Primary: Visit-to-visit variability (VVV) of blood pressure Secondary: Not reported	Primary: Each measure of VVV of SBP was lower among participants randomized to chlorthalidone and amlodipine compared with those randomized to lisinopril. All four VVV of SBP metrics were lower among participants randomized to amlodipine vs chlorthalidone after full multivariable adjustment. After multivariable adjustment including mean SBP across visits and compared with participants randomized to chlorthalidone, participants randomized to amlodipine had a 0.36 (standard error [SE]: 0.07) lower standard deviation (SD) of SBP and participants randomized to lisinopril had a 0.77 (SE=0.08) higher SD of SBP. Results were consistent using other VVV of SBP metrics. These data suggest chlorthalidone and amlodipine are associated with lower VVV of SBP than lisinopril. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Bangalore et al.[24] (2017) ALLHAT Chlorthalidone 12.5 to 25 mg/day vs amlodipine 2.5 to 10 mg/day vs lisinopril 10 to 40 mg/day	Post-hoc analysis of ALLHAT Patients in ALLHAT with average blood pressure ≥140 mmHg systolic or ≥90 mm Hg diastolic on ≥3 antihypertensive medications, or blood pressure <140/90 mmHg on ≥4 antihypertensive medications (i.e., identified as having apparent treatment-resistant hypertension) at 2-year follow up	N=14,684 4.9 years (mean)	Primary: Combined fatal CHD or nonfatal MI Secondary: All-cause mortality, fatal and nonfatal stroke, combined CHD, combined cardiovascular disease (combined CHD, stroke, treated angina without hospitalization, heart failure, and PAD)	Primary: Of participants assigned to chlorthalidone, amlodipine, or lisinopril, 9.6%, 11.4%, and 19.7%, respectively, had treatment-resistant hypertension. During mean follow-up of 2.9 years, primary outcome incidence was similar for those assigned to chlorthalidone compared with amlodipine or lisinopril (amlodipine- vs chlorthalidone-adjusted HR, 0.86; 95% CI, 0.53 to 1.39; P=0.53; lisinopril- vs chlorthalidone-adjusted HR, 1.06; 95% CI, 0.70 to 1.60; P=0.78). Secondary: Secondary outcome risks were similar for most comparisons except coronary revascularization, which was higher with amlodipine than with chlorthalidone (HR, 1.86; 95% CI, 1.11 to 3.11; P=0.02). An as-treated analysis based on diuretic use produced similar results.
Pupita et al.[25] (1983) Chlorthalidone 50 mg QD vs furosemide 25 mg QD	RCT, XO Men and women with a mean age of 53.9±9.2 years with mild to moderate HTN	N=36 12 months	Primary: Blood pressure Secondary: Plasma electrolytes, adverse events	Primary: Patients taking chlorthalidone had significantly lower SBP at each monthly measurement compared to baseline (P<0.01). However, only DBP values at month five were significant compared to baseline (P<0.05). Patients taking furosemide had significantly lower SBP at months three, four, and five compared to baseline (P<0.05 for month three, and P<0.01 for months four and five). DBP values were significantly lower at all monthly measurements compared to baseline in patients taking furosemide (P<0.01). At month one, SBP decreased by 19.4 mm Hg with chlorthalidone and by 21.2 mm Hg with furosemide (P<0.001). DBP decreased by 11 mm Hg with chlorthalidone and by 12.6 mm Hg with furosemide at month one (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: There were no significant changes in serum sodium levels with either chlorthalidone or furosemide. Patients taking chlorthalidone had significantly lower serum chloride levels compared to baseline at all points (P<0.01), whereas patients taking furosemide had significantly lower levels only at month six (P<0.05). Both chlorthalidone and furosemide significantly reduced serum potassium levels at all points compared to baseline (P<0.01). Patient taking chlorthalidone reported adverse effects including dizziness, transient abdominal disorder, and slight weakness. Patients taking furosemide reported transient early weakness and irritability. The rate of adverse events was not statistically significant in either treatment group.
Bakris et al.[26] (2012) Azilsartan medoxomil and chlorthalidone (single pill) vs azilsartan medoxomil and HCTZ (co-administered) Treatments were titrated to a target of <140/90 mm Hg (or <130/80 mm Hg if diabetes of chronic kidney disease)	DB, RCT Patients aged ≥18 years with stage 2 primary HTN	N=609 10 weeks (after 2 week placebo run-in)	Primary: Change in trough, seated clinic systolic blood pressure at weeks 6 and 10 Secondary: Change from baseline in clinic DBP and 24-hour mean systolic and diastolic blood pressures by ambulatory blood pressure monitoring	Primary: Change in SBP at week six demonstrated a mean difference of -5.6 mm Hg (95% CI, -8.3 to -2.9; P<0.001) in favor of the chlorthalidone group. Fewer patients in the chlorthalidone group required titration to a higher dose of diuretic (P<0.001). At the end of week 10, a greater mean SBP reduction was maintained in the chlorthalidone group compared to the HCTZ group (-5.0 mm Hg; 95% CI, -7.5 to -2.5; P<0.001). Secondary: The chlorthalidone group demonstrated a significantly greater reduction in 24-hour mean SBP at weeks six and 10. For both clinica and 24-hour mean DBP, greater blood pressure reduction was observed in the chlorthalidone group compared to the HCTZ group at both study points.
Ernst et al.[27] (2006)	RCT, SB, XO	N=30	Primary: Comparison of the	Primary: At week eight, there was a greater reduction in 24-hour mean SBP with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Chlorthalidone 12.5 mg in the morning vs HCTZ 25 mg in the morning At week 4, both HCTZ and chlorthalidone were titrated to 50 mg in the morning and 25 mg in the morning, respectively for the remainder of the trial.	Men and women aged 18 to 79 years with pre-HTN or a new or established diagnosis of HTN (stage 1 or 2), not receiving antihypertensive medications, and had an average office blood pressure value in the last 6 months between 140 and 179 mm Hg systolic or 90 and 109 mm Hg diastolic	8 weeks plus 4 week washout period	change in 24-hour mean SBP and DBP from baseline to week 8 Secondary: Comparison of changes in mean SBP and mean DBP for office blood pressure at each visit, change in ambulatory daytime and nighttime mean SBP and DBP from baseline to week 8, development of hypokalemia	chlorthalidone 25 mg/day compared to HCTZ 50 mg/day compared to baseline (-12.4±1.8 vs -7.4±1.7 mm Hg, respectively; P=0.054). Secondary: There was a trend in favor of greater reduction in SBP with chlorthalidone than with HCTZ at each office visit. However, the difference was only statistically significant at week 2 (-15.7±2.2 vs -4.5±2.1 mm Hg, respectively; P=0.001). Although mean reductions in DBP was also greater with chlorthalidone compared to HCTZ at each study visit, the differences were not statistically significant at any visit (P>0.89 for all). The reduction in SBP during nighttime hours was -13.5±1.9 mm Hg for chlorthalidone and -6.4±1.7 mm Hg for HCTZ (P=0.009). The reduction in daytime mean SBP between both groups was not significantly different (-11.4±2.0 vs -8.1±1.9 mm Hg, respectively; P=0.230). Changes in serum potassium were similar between treatment groups (P=0.76). The incidence of hypokalemia was 50% in patients taking HCTZ and 46% in patients taking chlorthalidone (P=0.682).
Carter et al.[28] (2004) Chlorthalidone 12.5 to 600 mg/day vs HCTZ 12.5 to 450 mg/day	MA Included trials which evaluate the pharmacokinetic and blood pressure lowering effects of chlorthalidone and HCTZ	N=200 Duration varied per study	Primary: Blood pressure Secondary: Serum potassium	Primary: In a dose equivalence study comparing HCTZ 100 mg QD to chlorthalidone 50 mg QD, blood pressure (SBP/DBP) reduced by 18/8 and 25/10 mm Hg compared to baseline, respectively. In another study comparing HCTZ 25 mg and triamterene 50 mg QD, HCTZ 50 mg and triamterene 100 mg QD, and chlorthalidone 50 mg QD, the blood pressure reduction was 15/8, 18/12, and 25/16 mm Hg, respectively. One other dose equivalence study comparing HCTZ 50 mg BID and chlorthalidone 50 mg QD, blood pressure reduction was 22/16 and 18/15 mm Hg, respectively. All available studies were inspected and it was concluded that HCTZ 50 mg is approximately equivalent to chlorthalidone 25 to 37 mg.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Furthermore, it was suggested that chlorthalidone doses should generally be approximately 50% to 75% of the typical HCTZ dose. Secondary: In a study comparing HCTZ 100 mg QD and chlorthalidone 50 mg QD, potassium increased slightly with chlorthalidone (0.02 mEq/L) and decreased significantly with HCTZ (0.22 mEq/L; P=0.009). However, in another study comparing HCTZ 50 mg BID and chlorthalidone 50 mg QD, serum potassium decreased by 0.38 mEq/L with HCTZ and by 0.03 mEq/L with chlorthalidone. The difference was not statistically significant (P<0.07).
Karotsis et al.[29] (2006) Chlorthalidone 12.5 mg QD vs felodipine 5 mg QD vs lisinopril 10 mg QD vs valsartan 80 mg QD All patients also received diltiazem 240 mg QD.	RCT Patients 25 to 79 years of age with uncontrolled HTN (average office blood pressure >140/90 mm Hg for all or >153/85 mm Hg for diabetics or patients <65 years of age, confirmed on 2 office visits ≥1 week apart) after ≥4 weeks of OL monotherapy with diltiazem at 240 mg QD	N=211 8 weeks	Primary: Blood pressure Secondary: Not reported	Primary: There was a significant decline in both office and home SBP and DBP during the trial with all treatments. The antihypertensive effect was more pronounced and reached significance when home blood pressure monitoring was used in comparison to office blood pressure without the white-coat effect (P<0.001 for all blood pressure changes). With or without the white-coat effect, blood pressure still declined and the differences were significant (P<0.0001 for all blood pressure changes). Secondary: Not reported
Nissinen et al.[30]	DB, RCT	N=23	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1980) Atenolol 100 mg QD plus chlorthalidone 25 mg in the morning vs atenolol and chlorthalidone 100-25 mg in the morning (fixed-dose combination product) vs placebo	Patients with newly diagnosed mild to moderate HTN (supine DBP 100 mm Hg on ≥3 occasions)	16 weeks	Changes in blood pressure and heart rate Secondary: Not reported	Each of the active drug combinations lowered standing, supine, and post-exercise blood pressure significantly compared to placebo at two and four weeks (P<0.001, P<0.01 and P<0.05). There was not a statistical difference between the active treatment regimens (P value not significant). Each of the active drug combinations lowered standing, supine, and post-exercise heart rate significantly compared to placebo at two and four weeks (P<0.001, P<0.01 and P<0.05). There was not a statistical difference between the active treatment regimens (P value not significant). Side effects did not differ between treatment groups and placebo in terms of frequency or severity. Reported side effects included dizziness, headache and tiredness. Secondary: Not reported
Fogari et al.[31] (1984) <u>Weeks 1 to 4:</u> chlorthalidone 12.5 mg QD vs atenolol 50 mg QD <u>Weeks 5 to study end:</u> atenolol and chlorthalidone 50-12.5 mg QD (fixed-dose combination	RCT, SB Patients 61 to 80 years inadequately controlled (SBP >170 mm Hg and/or DBP >100 mm Hg) on antihypertensive medications	N=38 6 months	Primary: Changes in blood pressure Secondary: Not reported	Primary: After the first four weeks, atenolol (from 177.5 to 161.1 mm Hg) significantly reduced blood pressure compared to baseline, but chlorthalidone did not (from 176.6 to 179.1 mm Hg). The combination atenolol-chlorthalidone therapy significantly reduced mean standing SBP and DBP, supine SBP and DBP, supine and standing heart rate, compared to previous therapies (P<0.001 for all comparisons). The combination atenolol-chlorthalidone therapy significantly reduced mean standing SBP and DBP, supine SBP and DBP, supine and standing heart rate, compared to atenolol and chlorthalidone monotherapy (P<0.001 or P<0.01 for all comparisons). Mean blood pressure reduction obtained by the atenolol and chlorthalidone combination product was 30/15 mm Hg in the standing position (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
product)				Serum potassium increased with atenolol-chlorthalidone (4.45 mEq/L) compared to chlorthalidone alone (4.01 mEq/L; P<0.001). Secondary: Not reported
Leonetti et al.[32] (1986) Atenolol 50 mg QD vs atenolol 100 mg QD vs chlorthalidone 12.5 mg QD vs atenolol and chlorthalidone 50-12.5 mg QD (fixed-dose combination product)	DB, RCT Patients 24 to 68 years with mild to moderate HTN (WHO stage I or II), with supine DBP ≥95 mm Hg at the end of the 4-week washout period	N=28 16 weeks	Primary: Changes in blood pressure Secondary: Not reported	Primary: Mean supine blood pressure was significantly reduced in all treatment groups compared to placebo: 153±18/93±9 mm Hg for atenolol 50 mg patients, 155±22/91±8 mm Hg for atenolol 100 mg patients, 148±17/93±11 mm Hg for chlorthalidone 12.5 mg patients, and 144±16/89±6 mm Hg for the atenolol-chlorthalidone combination patients. All of the changes in blood pressure were significant (P<0.01) versus placebo. Supine SBP was lower with atenolol-chlorthalidone than with the atenolol 100 mg alone (P<0.05). Upright SBP was lower with atenolol-chlorthalidone than with atenolol 50 mg alone (P<0.05) and atenolol 100 mg alone (P<0.05). Mean supine heart rate was 77±7 bpm after placebo which decreased to 69±10 bpm (P<0.01) after atenolol 50 mg, to 67±6 bpm (P<0.01) after atenolol 100 mg, to 77±10 bpm (P=not significant, was not reported) after chlorthalidone alone. Chlorthalidone alone demonstrated a significant reduction in serum potassium levels compared to placebo (3.88 vs 4.09 mEq/L; P<0.05) and no change when the atenolol-chlorthalidone combination was compared to placebo (3.98 vs 4.09; P=not significant, value was not reported). Chlorthalidone alone and atenolol-chlorthalidone demonstrated a significant increase in serum uric acid levels compared to placebo (4.90±1.52 mg/dL, 5.07±1.33 mg/dL, respectively, vs 4.24±1.12 for placebo; P<0.05 for both). All treatments were well tolerated. Some adverse events reported included dyspnea, precordial discomfort and cold extremities. Incidence, severity

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				and P values were not reported.
Finnerty et al.[33] (1980) Chlorthalidone 50 mg plus reserpine 0.25 mg vs HCTZ 50 mg plus reserpine 0.125 mg	DB Patients with essential HTN unresponsive to diet control and diuretic therapy	N=57 6 weeks	Primary: The change in mean DBP from baseline Secondary: Incidence of frequent or severe side effects	Primary: The chlorthalidone plus reserpine group had a mean decrease in DBP of 17.0 mm Hg at study endpoint compared with a mean decrease of 18.6 mm Hg in the HCTZ plus reserpine group. At study completion both treatment groups achieved diastolic control of at least 5 mm Hg below the targeted diastolic goal of 90 mm Hg. Secondary: There were no reports of frequent or severe side effects in either treatment group.
Akram et al.[34] (2007) NATIVE Indapamide SR 1.5 mg QD added to background antihypertensive therapy	OL Patients remaining hypertensive (145 to 180/95 to 105 mm Hg) while receiving an ACE inhibitor, β-blocker, calcium-channel blocker, ARBs, α-blocker, or other therapy	N=1,941 3 months	Primary: Blood pressure Secondary: Glucose and cholesterol levels	Primary: At three months, SBP and DBP both decreased significantly compared to baseline. SBP had a change from 166±16 mm Hg at baseline to 132±12 mm Hg at three months. DBP had a change from 102±8 mm Hg at baseline to 83±6 mm Hg at three months (P<0.0001 for both). At study end, 84% of patients achieved target SBP of ≤140 mm Hg and 61% achieved blood pressure normalization (SBP/DBP <140/90 mm Hg). Secondary: Glucose and cholesterol levels were unaffected by indapamide SR.
Beckett et al.[35] (2008) HYVET Indapamide 1.5 mg/day vs placebo Perindopril 2 to 4 mg/day or matching placebo	DB, MC, PC, RCT Patients ≥80 years (mean age 84 years) with sustained SBP ≥160 mm Hg	N=3,845 1.8 years (mean)	Primary: Fatal or nonfatal stroke Secondary: Death from any cause, death from cardiovascular causes, death from stroke	Primary: At two years, 73.4% of patients in the active-treatment groups were receiving indapamide plus perindopril. Mean blood pressure while sitting was 15.0/6.1 mm Hg lower with active-treatment than placebo. Active treatment was associated with a 30% reduction in the rate of fatal or nonfatal stroke (95% CI, -1 to 51; P=0.06). Secondary: Active treatment was associated with a 21% reduction in the rate of death from any cause (95% CI, 4 to 35; P=0.02), a 23% reduction in the rate of death from cardiovascular causes (95% CI, -1 to 40; P=0.06) and a 39% reduction in the rate of death from stroke (95% CI, 1 to 62; P=0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
was added if necessary to achieve the target blood pressure of 150/80 mm Hg.				Active treatment was associated with a 64% reduction in the rate of heart failure (95% CI, 42 to 78; P<0.001). Fewer serious adverse events were reported in the active-treatment group (358 vs 448; P=0.001).
Milia et al.[36] (2006) Indapamide 2.5 mg QD vs bendro-flumethiazide* 2.5 mg QD	DB, PG, PRO, RCT Ambulant patients with a first-ever minor hemispheric ischemic stroke or TIA	N=26 28 days	Primary: Blood pressure, cerebral blood flow Secondary: Not reported	Primary: Both indapamide and bendroflumethiazide significantly reduced blood pressure from baseline (-14.7±12.5 mm Hg and -7.7±9.16 mm Hg, respectively; P<0.001 and P=0.02, respectively). A nonsignificant trend toward greater blood pressure reduction was seen in patients taking indapamide. There were no statistically significant differences in blood pressure reduction between both treatment groups. There was a nonsignificant trend toward increases in blood flow in both treatment groups. However, there was no statistically significant differences in carotid blood flow between both treatment groups (P=0.04 for between-group comparison). Secondary: Not reported
Madkour et al.[37] (1996) Indapamide 2.5 mg QD vs HCTZ 50 mg QD	RCT Patients aged 32 to 70 years with impaired renal function for 1 to 15 years and moderate HTN for 2 to 27 years, initial creatinine clearance between 32 and 80 mL/min/1.73 m^2 BSA	N=28 24 months	Primary: Blood pressure, changes in creatinine clearance Secondary: Not reported	Primary: Blood pressure normalized in all patients taking either indapamide or HCTZ. There were no significant differences in SBP or DBP between groups. At 24 months, creatinine clearance progressively increased from 58±4.4 to 72±4.4 mL/min/1.73 m^2 BSA in patients treated with indapamide (P<0.01). Creatinine clearance progressively decreased from 65±3.0 to 53±3.0 mL/min/1.73 m^2 BSA in patients treated with HCTZ (P<0.01). Creatinine clearance significantly increased by 28.5±4.4% with indapamide and decreased by 17.4±3.0% with thiazide therapy (P<0.01). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
PROGRESS[38] (2001) Perindopril 4 mg/day vs perindopril 4 mg/day and indapamide 2 to 2.5 mg/day vs placebo	DB, MC, PC, RCT Patients with a history of prior stroke or TIA within the previous 5 years	N=6,105 4 years	Primary: Fatal or nonfatal stroke Secondary: Fatal or disabling stroke, total major vascular events comprising the composite of nonfatal stroke, nonfatal MI, or death due to any vascular cause (including unexplained sudden death); total and cause specific deaths; hospital admissions	Primary: Patients receiving active treatment experienced a 28% reduction in nonfatal or fatal stroke (95% CI, 17 to 38; P<0.0001). There were similar reductions in the risk of stroke in hypertensive and non-hypertensive subgroups (32 vs 27%; P<0.01) A trend towards a greater effect of active treatment among patients treated with combination therapy (43% risk reduction) than in those treated with single drug therapy (5% risk reduction) was reported. Secondary: There was a 33% reduction in fatal or disabling strokes in the active treatment group. Active treatment reduced the risk of total major vascular events by 26% (P=0.02). There were no significant differences between active treatment and placebo in total deaths from vascular or nonvascular causes. Among those assigned active treatment, there was a 9% RR reduction in hospitalization, with a median reduction of 2.5 days in the time spent in the hospital during follow-up. Combination therapy with perindopril plus indapamide reduced blood pressure by 12/5 mm Hg and stroke risk by 43%. Single drug therapy reduced blood pressure by 5/3 mm Hg and produced no discernible reduction in the risk of stroke.
Hua et al.[39] (1976) Metolazone 5 mg QD vs	XO Patients with HTN	N=20 Duration not specified	Primary: Blood pressure, serum potassium Secondary: Not reported	Primary: Blood pressures on metolazone tended to be lower than on chlorothiazide, but the difference was not statistically significant. Both agents significantly lowered serum potassium concentrations and total body potassium to a similar degree. However, the serum potassium did not fall below the normal range in any patient and no potassium supplements were required.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
chlorothiazide up to 5 g BID				Secondary: Not reported
ADVANCE Collaborative Group[40] (2007) Perindopril (2 to 4 mg) and indapamide (0.625 to 1.25 mg) QD vs placebo	DB, MC, PC, RCT Adults 55 years of age or older who were diagnosed with type 2 diabetes at age 30 or older, and a history of cardiovascular disease or ≥1 other risk factor for cardiovascular disease	N=11,140 Mean 4.3 years	Primary: Composites of major macrovascular and microvascular events (death from cardiovascular disease, nonfatal stroke, nonfatal MI, or new renal or diabetic eye disease) Secondary: Macrovascular and microvascular endpoints analyzed separately	Primary: The relative risk of a major macrovascular or microvascular event was reduced by 9% (861 [15.5%] active vs 938 [16.8%] placebo; HR, 0.91, 95% CI 0.83 to 10, P=0.04). Secondary: The RR of death from cardiovascular disease was reduced by 18% (211 [3.8%] active vs 257 [4.6%] placebo; 0.82, 0.68-0.98, p=0.03) and death from any cause was reduced by 14% (408 [7.3%] active vs 471 [8.5%] placebo; 0.86, 0.75-0.98, P=0.03).
Hansson et al.[41] (2000) NORDIL Conventional therapy (diuretic, β-blocker or both) vs diltiazem 180 to 360 mg QD	BE, MC, OL, PRO, RCT Patients 50 to 74 years of age with DBP ≥100 mm Hg and previously untreated	N=10,881 4.5 years	Primary: Combined fatal and nonfatal stroke, fatal and nonfatal MI, other cardiovascular death Secondary: Fatal plus nonfatal stroke and fatal plus nonfatal MI	Primary: The primary endpoint occurred in 403 of the diltiazem patients and 400 of the diuretic/β-blocker patients (RR, 1.00; 95% CI, 0.87 to 1.15; P=0.97). Secondary: Rates of secondary endpoints were similar between the groups. Fatal plus nonfatal stroke occurred in 159 of the diltiazem patients and 196 of the diuretic/β-blocker patients (P=0.04). Fatal plus nonfatal MI occurred in 183 of the diltiazem patients and 157 of the diuretic/β-blocker patients (P=0.17). Other endpoints were not statistically different between the groups including cardiovascular death (P=0.41), all cardiac events (P=0.57 and congestive heart failure (P=0.42).
Ames[42]	MA (13 trials)	N=1,547	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1996) Indapamide 2.5 mg QD vs HCTZ ≤25 mg or its equivalent in other thiazides, up to 112.5 mg QD	Patients with HTN	1 to 25 months	Comparison of the effects of thiazides and indapamide on blood lipids and blood pressure Secondary: Not reported	The mean change from baseline was 1.4% for TC, 5.5% for HDL-C, and -0.5% for TG with indapamide. None of the differences were statistically significant. Low-dose thiazide therapy did not decrease TC at any data point. The mean percent increase in TC was 3.8%, in HDL-C was 3.1%, and in TG was 10.8% with low-dose HCTZ. The increases in TC and TG from baseline was statistically significant (P<0.01). The mean change in TC was 6.3%, in HDL-C was -0.5%, and in TGs was 19.5% for higher doses of HCTZ. Increases from baseline in TC and TG were statistically significant. SBP decreased more with higher doses of HCTZ than with low-dose thiazide therapy (P<0.05). The effects of indapamide on systolic arterial pressure were intermediate between, and not statistically different from, either thiazide dose. Decreases in DBP did not differ among groups. Secondary: Not reported
Messerli et al.[43] (1998) Diuretics (amiloride, chlorthalidone, HCTZ, HCTZ and triamterene [fixed-dose combination product], or thiazide) vs β-blockers (atenolol, metoprolol or	MA 10 RCTs lasting ≥1 year, which used as first line agents diuretics and/or β-blockers and reported morbidity and mortality outcomes in patients ≥60 years of age with HTN	N=16,164 1 year	Primary: Cardiovascular morbidity and mortality, all-cause morbidity Secondary: Not reported	Primary: Diuretic treatment significantly reduced the odds for cardiovascular mortality by 25% (OR, 0.75; 95% CI, 0.64 to 0.87), while β-blockers did not reduce cardiovascular mortality (OR, 0.98; 95% CI, 0.78 to 1.23; P values not reported). Diuretic treatment significantly reduced the odds for all-cause mortality by 14% (OR, 0.86; 95% CI, 0.77 to 0.96), while β-blockers did not reduce all-cause mortality (OR, 1.05; 95% CI, 0.88 to 1.25; P values not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
pindolol)				
Baguet et al.[44] (2007) Antihypertensive drugs (enalapril, ramipril, trandolapril, candesartan, irbesartan, losartan, olmesartan, telmisartan, valsartan, HCTZ, indapamide SR*, atenolol, amlodipine, lercanidipine*, manidipine*, enalapril, ramipril, trandolapril, and aliskiren) Drugs were used as monotherapy, either at a fixed daily dosage or in increasing dosages. Although cicletanine*, furosemide and spironolactone were considered for inclusion, none of the trials	MA Patients greater than 18 years of age with mild or moderate essential HTN (SBP 140 to 179 mm Hg and/or DBP 90 to 109 mm Hg)	N=10,818 8 to 12 weeks	Primary: Weighted average reductions in SBP and DBP Secondary: Not reported	Primary: Data did not reflect outcomes from direct, head-to-head comparative trials or formal comparisons between drugs. Diuretics (-19.2 mm Hg; 95% CI, -20.3 to -18.0), calcium channel blockers (-16.4 mm Hg; 95% CI, -17.0 to -15.8) and ACE inhibitors (-15.6 mm Hg; 95% CI, -17.6 to -13.6) produced the greatest reductions in SBP from baseline (P values not reported). The magnitude of DBP reductions were generally similar among all drug classes; however, the greatest reductions in DBP from baseline were observed with the β-blocker, atenolol (-11.4 mm Hg; 95% CI, -12.0 to -10.9), calcium channel blockers (-11.4 mm Hg; 95% CI, -11.8 to -11.1) and diuretics (-11.1 mm Hg; 95% CI, -11.7 to -10.5) (P values were not reported). The weighted average reduction of SBP and DBP for each drug class were as follows: Diuretics: -19.2 (95% CI, -20.3 to -18.0) and -11.1 mm Hg (95% CI, -11.7 to -10.5), respectively. β-blockers: -14.8 (95% CI, -15.9 to -13.7) and -11.4 mm Hg (95% CI, -12.0 to -10.9), respectively. Calcium channel blockers: -16.4 (95% CI, -17.0 to -15.8) and -11.4 mm Hg (95% CI, -11.8 to -11.1), respectively. ACE inhibitors: -15.6 (95% CI, -17.6 to -13.6) and -10.8 mm Hg (95% CI, -11.9 to -9.7), respectively. ARBs: -13.2 (95% CI, -13.6 to -12.9) and -10.3 mm Hg (95% CI, -10.5 to -10.1), respectively. Renin inhibitor: -13.5 (95% CI, -14.2 to -12.9) and -11.3 mm Hg (95% CI, -11.7 to -10.9), respectively. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
relating to these agents satisfied all inclusion criteria.				

*Agent not available in the United States.
Drug regimen abbreviations: BID=twice daily, QD=once daily, SR=systematic review
Study design abbreviations: BE=blinded endpoint, DB=double blind, MA=meta analysis, MC=multicenter, OL=open label, PC=placebo controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, SB=single blind, XO=cross over
Miscellaneous abbreviations=ACE inhibitors=angiotensin converting enzyme inhibitors, ARB=angiotensin II receptor blocker, BSA=body surface area, CHD=coronary heart disease, CI=confidence interval, DBP=diastolic blood pressure, HCTZ=hydrochlorothiazide, HR=hazard ratio, HTN=hypertension, MI=myocardial infarction, PAD=peripheral artery disease, RR=relative risk, SBP=systolic blood pressure, TC=total cholesterol, TG=triglycerides, TIA=transient ischemic attack, WHO=World Health Organization

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 10. Relative Cost of the Thiazide-Like Diuretics

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Chlorthalidone	tablet*	Thalitone®	$$$$	$
Indapamide	tablet*	N/A	N/A	$
Metolazone	tablet*	N/A	N/A	$

*Generic is available in at least one dosage form or strength.
N/A=Not available

X. Conclusions

The thiazide-like diuretics are approved for the treatment of hypertension and edema associated with congestive heart failure. Chlorthalidone and metolazone are also indicated for the treatment of edema due to renal dysfunction. Additionally, chlorthalidone is approved for the adjunctive treatment of edema associated with hepatic cirrhosis, as well as corticosteroid and estrogen therapy.[1-4] All of the agents are available in a generic formulation.

Guidelines recommend the use of diuretics and sodium restriction for the management of ascites due to cirrhosis. Spironolactone is recommended as first-line therapy, either as monotherapy or in combination with furosemide. Amiloride or eplerenone are alternative treatment options in patients experiencing gynecomastia with spironolactone.[16]

For the treatment of chronic heart failure, guidelines recommend the use of diuretics in all patients who have evidence of volume overload. Loop diuretics are generally recommended as initial therapy in patients with left ventricular dysfunction. For those with persistent fluid retention despite treatment with a loop diuretic, a thiazide diuretic or metolazone may be added to the regimen. In patients with normal left ventricular function, either a thiazide diuretic or loop diuretic may be used as initial therapy to manage fluid overload.[7-9]

There are several national and international organizations that have published guidelines on the treatment of hypertension. Thiazide-type diuretics are frequently recommended as initial therapy in patients with uncomplicated hypertension.[7-13] According to the National Heart, Lung, and Blood Institute's Eighth Report of The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8), thiazide-type diuretics should be utilized first-line for most patients with hypertension, either alone or in combination with another hypertensive from a different medication class (e.g., ACE inhibitors, ARBs, β-blockers, calcium channel blockers).[7] Several guidelines consistently recommend that the selection of an antihypertensive agent be based on compelling indications for use.[7-15] Most patients will require more than one antihypertensive medication to achieve blood pressure goals.[7-13]

In clinical trials, the thiazide-like diuretics have been shown to effectively lower blood pressure.[17-44] There were no studies found in the medical literature that directly compared the efficacy and safety of the thiazide-like diuretics for the treatment of hypertension.

There is insufficient evidence to support that one brand thiazide-like diuretic is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand thiazide-like diuretics within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand thiazide-like diuretic is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Vasopressin Antagonists
AHFS Class 402828
May 8, 2024

I. Overview

Conivaptan is an injectable product that is Food and Drug Administration (FDA)-approved for the treatment of euvolemic and hypervolemic hyponatremia in hospitalized patients. Conivaptan is not indicated for the treatment of congestive heart failure as the effectiveness of this agent has not been established in such patients.[1] Tolvaptan is an oral vasopressin antagonist that is FDA-approved for the treatment of clinically significant euvolemic and hypervolemic hyponatremia (serum sodium <125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure and Syndrome of Inappropriate Antidiuretic Hormone (SIADH).[2] The major disorders associated with euvolemic hyponatremia include SIADH, nephrogenic syndrome of inappropriate antidiuresis (NSIAD), glucocorticoid deficiency, hypothyroidism, exercise-associated hyponatremia (EAH), low solute intake, and primary polydipsia. Hypervolemic hyponatremia is most often caused by heart failure, cirrhosis, nephrotic syndrome, as well as acute and chronic renal failure.[3] Tolvaptan is now also available under the brand name Jynarque®, which is indicated to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD).[4] ADPKD is a hereditary disease characterized by renal cysts that are visible by ultrasonographic imaging studies. Patients with ADPKD can present with hypertension, hematuria, proteinuria, or kidney function impairment, detected by routine laboratory examinations. Flank pain is the most common symptom reported by patients.[5] ADPKD slowly progresses to chronic kidney disease and ultimately end-stage renal disease.[5]

Hyponatremia is frequently associated with elevated plasma levels of arginine vasopressin (AVP). AVP is normally secreted in response to increased plasma osmolality, decreased blood volume, or decreased blood pressure. Suppression of AVP secretion occurs when osmolality falls below a certain threshold, which results in renal excretion of free water. Failure to suppress AVP secretion may result in water retention and hyponatremia.[3] The use of traditional diuretics leads to both water and electrolyte excretion (diuresis); whereas, the use of tolvaptan leads to an increase in water excretion only (aquaresis), a decrease in urine osmolality, and an increase in serum sodium concentration. Urinary excretion of sodium and potassium, as well as plasma potassium concentrations, are not significantly affected by tolvaptan.[2]

The management of hyponatremia depends on the clinical presentation and duration of the disease (acute versus chronic hyponatremia). Therapeutic options include treating the underlying disease (if possible), fluid restriction, sodium chloride administration, and diuresis. Patients with chronic mild hyponatremia are often asymptomatic and treatment consists of fluid restriction or isotonic saline administration.[6] Acute severe hyponatremia requires more aggressive initial therapy as it may increase morbidity and mortality. Treatment of hyponatremia must be approached carefully as overly rapid correction may cause osmotic demyelination. Symptoms of osmotic demyelination are often irreversible and include quadriparesis, paraparesis, dysphagia, dysarthria, diplopia, seizures, coma, and death.[3,6]

The vasopressin antagonists that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Tolvaptan is available in a generic formulation. This class was last reviewed in May 2022.

Table 1. Vasopressin Antagonists Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Conivaptan	injection^	Vaprisol®	none
Tolvaptan	tablet	Jynarque®, Samsca®*	tolvaptan

*Generic is available in at least one dosage form or strength.
^Product is primarily administered in an institution.
PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the vasopressin antagonists are summarized in Table 2.

Table 2. Treatment Guidelines Using the Vasopressin Antagonists

Clinical Guideline	Recommendation(s)
American Journal of Medicine: **Diagnosis, Evaluation, and Treatment of Hyponatremia: Expert Panel Recommendations (2013)**[3]	<u>General information</u> • There are no data to suggest that the etiology of the hyponatremia, nor the methodology used to correct hyponatremia, alters the susceptibility for producing osmotic demyelination with overly rapid correction. • The rate of correction of hyponatremia must be taken into account before deciding on the most appropriate therapy for any patient with hyponatremia. • Patients with acute (<48 hours) hyponatremia may present with alarming neurologic findings, and they sometimes die of brain herniation. When hyponatremia develops over several days, brain swelling is minimized so that patients with chronic (<48 hours) hyponatremia have more modest symptoms and almost never die of brain herniation. <u>Rate of correction of hyponatremia</u> • To reverse serious manifestations of acute hyponatremia, increasing serum sodium by 4 to 6 mmol/L is sufficient to prevent brain herniation and neurological damage from cerebral ischemia. • The rate of correction does not need be restricted in patients with true acute hyponatremia, nor is re-lowering of excessive corrections indicated; however, if there is any uncertainty as to whether the hyponatremia is chronic versus acute, then the limits for correction of chronic hyponatremia should be followed. • In patients with chronic hyponatremia, neurologic sequelae are associated with more rapid rates of correction. The osmotic demyelination syndrome (ODS) can usually be avoided by limiting correction of chronic hyponatremia to 4 to 8 mmol/L in 24 hours for those at low-risk of ODS and to 4 to 6 mmol/L/day for those at high-risk. • Limits not to exceed: 8 mmol/L in any 24-hour period for high-risk patients and 10 to 12 mmol/L in any 24-hour period or 18 mmol/L in any 48-hour period in patients at normal risk. • Factors that place patients at high risk of developing ODS include serum sodium concentration ≤105 mmol/L, hypokalemia, alcoholism, malnutrition, and advanced liver disease. <u>Conventional therapy of euvolemic hyponatremia</u> • Treatment of patients with euvolemic hyponatremia will vary greatly depending on their presentation. The single most important factor guiding initial therapy is the presence of neurologic symptoms. • Cases of acute hyponatremia (≤48 hours in duration) are usually symptomatic if the hyponatremia is severe (≤120 mmol/L). These patients are at greatest risk from neurologic complications from the hyponatremia itself and should be corrected to higher serum sodium levels promptly. • Patients with more chronic hyponatremia (>48 hours in duration) who have minimal neurologic symptomatology are at little risk from complications of hyponatremia itself, but can develop osmotic demyelination following rapid correction. There is no indication to correct these patients rapidly, and they should be treated using slower-acting therapies. • Syndrome of inappropriate antidiuretic hormone secretion: ○ Correction of acute symptomatic hyponatremia is best accomplished with hypertonic (3%) saline given via bolus or continuous infusion. Intravenous furosemide 20 to 40 mg should be used to treat volume overload. Acute treatment should be discontinued when the patient's symptoms are abolished, a safe serum sodium level (≥120 mmol/L) is achieved, or a total

Clinical Guideline	Recommendation(s)
	correction of 18 mmol/L is achieved. o For the treatment of mild-to-moderate chronic hyponatremia, fluid restriction represents the least toxic therapy, and has generally been the treatment of choice. Several days of restriction are usually necessary before a significant increase in plasma osmolality occurs. o Pharmacologic interventions are reserved for refractory cases where the degree of fluid restriction required to avoid hypo-osmolality is so severe that the patient is unable, or unwilling, to maintain it. The preferred drug is demeclocycline, which causes a nephrogenic form of diabetes insipidus. Treatment must be continued for several days to achieve maximal diuretic effects. Other agents, such as lithium, have similar renal effects but are less desirable because of inconsistent results and significant side effects and toxicities. Urea is as an alternative treatment for syndrome of inappropriate antidiuretic hormone secretion. • Glucocorticoid deficiency: o Glucocorticoid replacement should be started immediately after completion of a rapid adrenocorticotropic hormone stimulation test. Several days of glucocorticoids are sometimes required for normalization of the plasma osmolality. Primary treatment of hyponatremia may be indicated if significant neurologic symptoms are present. • Hypothyroidism: o The primary therapy of hypothyroidism is thyroid hormone replacement. o Hyponatremia with hypothyroidism is infrequent and generally of mild severity; therefore, modest fluid restriction is generally the only treatment necessary. o Symptomatic hyponatremia may be seen in patients with more severe hypothyroidism and altered mental status, primary treatment of hyponatremia may be indicated to ascertain whether the hyponatremia is contributing to the patient's neurologic symptoms. • Exercise-associated hyponatremia (EAH): o EAH can be severe and life threatening as a result of cerebral edema and noncardiogenic pulmonary edema. o Hyponatremia occurring in the setting of endurance exercise is acute, and treatment of symptomatic hyponatremia should be rapid. o With significant central nervous system impairment, hypertonic saline should begin immediately and continued until the serum sodium reaches 125 mmol/L or symptoms resolve. • Low solute intake: o Hyponatremia from low solute intake is corrected by instituting proper nutrition, with increased content of solute both as electrolytes and protein. • Primary polydipsia: o Therapy should be directed at reducing fluid intake into the normal range. o Fluid ingestion in patients with psychogenic causes of polydipsia responds variably to behavior modification and pharmacologic therapy (e.g., clozapine). <u>Conventional therapy of hypervolemic hyponatremia</u> • For all diseases associated with edema formation, dietary sodium restriction and diuretic therapy are the mainstays of therapy. • Congestive heart failure (CHF): o For severely symptomatic patients with very low or rapidly falling serum sodium, treatment should consist of hypertonic (3%) NaCl combined with loop diuretics to prevent fluid overload; for patients with mild to moderate symptoms, begin with fluid restriction (1 L/d total) and, if signs of volume overload are present, administer loop diuretics. o If the serum sodium does not correct to the desired level, lift the fluid

Clinical Guideline	Recommendation(s)
	restriction and start either conivaptan (if intravenous route is preferred or required) or tolvaptan (if oral therapy is preferred). o Hyponatremia in HF is almost always chronic, so current limits for rate of correction of chronic hyponatremias should be observed. o If tolvaptan is used, it may be up-titrated from 15 to 30 to 60 mg/d as necessary to achieve the desired level of correction of serum sodium. o Continue treatment until the serum sodium has either normalized, symptoms have improved, or the level of serum sodium is no longer compromising administration of needed diuretic therapy. • The stimuli for AVP secretion may be more dynamic than in other disease states; if prescribed after discharge, assessing the need for chronic therapy of hyponatremia by providing a window of observation off therapy two to four weeks after treatment initiation is a reasonable approach. • Cirrhosis: o There are no guidelines specifically regarding treatment of hyponatremia in cirrhosis. o Demeclocycline is relatively contraindicated because of a high incidence of nephrotoxicity, and urea has not been used often. Fluid restriction is the usual approach, but without outcome studies to assess its effectiveness. • Nephrotic syndrome, acute and chronic renal failure: o In patients with hyponatremia with advanced acute and chronic renal failure and glomerular filtration rate <20 mL/min, fluid restriction to amounts less than insensible losses plus urine output is generally necessary to cause a negative solute-free water balance and correction of hyponatremia. o Vaptans can be employed in selected cases where fluid restriction is not successful or not well tolerated. <u>Use of vasopressin receptor antagonists in hyponatremia</u> • Exclude hypovolemic hyponatremia. • Do not use in conjunction with other treatments for hyponatremia. • Do not use immediately after cessation of other treatments for hyponatremia, particularly 3% NaCl. • Monitor serum sodium closely (every 6 to 8 hours) for the first 24 to 48 hours after initiating treatment. • Maintain ad libitum fluid intake during the first 24 to 48 hours of treatment; hyponatremia can correct too quickly with coincidental fluid restriction; in patients with a defective or impaired thirst mechanism (e.g., intubated or unconscious patients), provide sufficient fluid to prevent overly rapid correction due to unopposed aquaresis. • Increase the frequency of serum sodium monitoring and consider stopping the vaptan if there is a change or deterioration in the patient's condition (e.g., nothing-by-mouth status, intubation) that limits the ability to request, access, or ingest fluid. • Severe, symptomatic hyponatremia should be treated with 3% NaCl, as this provides a quicker and more certain correction of serum sodium than vaptans. • Currently, there are insufficient data for use of vaptans in severe asymptomatic hyponatremia (serum sodium <120 mmol/L)—use vaptans with caution and with more frequent monitoring in these patients. • If overcorrection occurs, consider re-lowering the serum sodium to safe limits. • For the treatment of acute severe hyponatremia, there is insufficient data from clinical trials to know if sufficiently rapid correction can be achieved with vasopressin receptor antagonists without the use of hypertonic saline. • Most studies to date in patients with hyponatremia have only been of relatively short duration. The most appropriate way to use these agents, their long-term response rates, how important the role of water restriction will remain during chronic use, and whether correction of chronic hyponatremia will result in improved cognitive

Clinical Guideline	Recommendation(s)
	function as suggested by 30-day studies of tolvaptan, and quality of life, or functional status, as suggested by initial studies of gait stability and falls, are unknown at the present time and will require additional study. • Safety issues must be considered carefully with any new class of drugs. The possibility of overcorrection has been of significant concern in all of the vasopressin receptor antagonist clinical trials, but to date osmotic demyelination has not been reported with any agent. The potential for serious drug interactions via interference with cytochrome P450 3A4-mediated metabolism of other drugs must also be recognized. Whether there will be any adverse effect of V_2 receptor inhibition in vascular endothelium is unknown. • Further studies will be needed to assess the appropriate use of vasopressin receptor antagonists, such as for correction of symptomatic hyponatremia either alone or in conjunction with hypertonic saline infusions; to assess the benefits of correction of hyponatremia in hospitalized patients in terms of disease outcomes and decreased lengths of intensive care unit and hospital stay; and for long-term treatment of minimally symptomatic hyponatremia in order to decrease the risks of neurocognitive dysfunction and gait instability.
Canadian Expert Consensus: **Updated Canadian Expert Consensus on Assessing Risk of Disease Progression and Pharmacological Management of Autosomal Dominant Polycystic Kidney Disease (2018)[9]**	• All patients with a diagnosis of Autosomal Dominant Polycystic Kidney Disease (ADPKD) or suspected ADPKD should be referred to a nephrologist for initial assessment. Initial assessment should include kidney imaging and, in some cases, genetic testing to determine the patient's risk of rapid progression and to determine what treatment should be initiated. • Patients with ADPKD who are <50 years old with eGFR >60 mL/min/1.73 m^2 and without significant cardiovascular comorbidities should have a target blood pressure of ≤110/75 mm Hg, realizing that in some patients an individual target may be needed. • Consider treatment with tolvaptan for patients who fulfill the enrollment criteria of the TEMPO 3:4 study: 18 to 50 years of age with total kidney volume (TKV) >750 mL and eGFR >45 mL/min/1.73 m^2. • Treatment with tolvaptan is recommended for patients who fulfill the enrollment criteria of the REPRISE study: o 18 to 55 years of age with eGFR of 25 to 65 mL/min/1.73 m^2 OR o 56 to 65 years of age with eGFR of 25 to 44 mL/min/1.73 m^2 with historical evidence of a decline in eGFR >2.0 mL/min/1.73 m^2/year. o Although there were no inclusion criteria for kidney size, based on the abundance of evidence that increased size of kidneys is relevant, these REPRISE criteria relate to those patients with ADPKD who have enlarged kidneys. In those patients with advanced or rapidly progressive chronic kidney disease (CKD) without enlarged kidneys, an alternate diagnosis for CKD should be investigated. • Treatment with tolvaptan is suggested for patients who, according to the Mayo Clinic Classification, are classified as 1D or 1E with eGFR in CKD stages 1 to 4 (eGFR >25 mL/min). Treatment with tolvaptan may be considered for patients who are classified as 1C and are <50 years old or have other risk factors for rapid progression, such as an annual decrease in eGFR of >2.5 mL/min/1.73 m^2 and/or increase in TKV of >5% per year. • Treatment with tolvaptan should be stopped when the patient develops ESRD. In the predialysis setting with eGFR <25 mL/min/1.73 m^2, there are no data to guide when treatment with tolvaptan should be stopped. • Additional considerations when giving tolvaptan: o Patients with ADPKD on treatment with tolvaptan should follow a sodium-restricted diet of ≤2.4 g/day (≤100 mmol/day). o Titrating tolvaptan to the maximal tolerated dose or to achieve a uOSM <250 mOsm/kg water is suggested. Consideration should be given to consultation with a dietician to minimize sodium and osmolal intake to help manage severe aquaretic adverse events.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the vasopressin antagonists are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Vasopressin Antagonists[2]

Indication	Tolvaptan*†
To slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease	✔ (Jynarque®)
Treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium <125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure and Syndrome of Inappropriate Antidiuretic Hormone	✔

*Patients requiring intervention to raise serum sodium urgently to prevent or to treat serious neurological symptoms should not be treated with tolvaptan.
†It has not been established that tolvaptan provides a symptomatic benefit to patients.

IV. Pharmacokinetics

The pharmacokinetic parameters of the vasopressin antagonists are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Vasopressin Antagonists[7]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Tolvaptan	≥40	99	Liver, extensive (% not reported)	Non-renal routes	12

V. Drug Interactions

Major drug interactions with the vasopressin antagonists are listed in Table 5. Tolvaptan is metabolized by cytochrome P450 (CYP) 3A, and use with strong CYP3A inhibitors causes a marked (5-fold) increase in exposure. Tolvaptan is contraindicated in combination with strong cytochrome CYP3A inhibitors, such as clarithromycin, ketoconazole, itraconazole, ritonavir, indinavir, nelfinavir, saquinavir, nefazodone, and telithromycin. The use of tolvaptan in combination with CYP3A inducers and moderate CYP3A inhibitors should also be avoided.[2,4]

Table 5. Major Drug Interactions with the Vasopressin Antagonists[7]

Generic Name	Interaction	Mechanism
Vasopressin antagonists (tolvaptan)	HIV protease inhibitors	Inhibition of CYP3A4 by HIV protease inhibitors may decrease the metabolic elimination of tolvaptan. Plasma concentrations and pharmacologic effects of tolvaptan may be increased by HIV protease inhibitors.
Vasopressin antagonists (tolvaptan)	Imidazoles	Inhibition of CYP3A4 by imidazoles may decrease the metabolic elimination of tolvaptan. Plasma concentrations and pharmacologic effects of tolvaptan may be increased by imidazoles.
Vasopressin antagonists (tolvaptan)	Macrolides and ketolides	Inhibition of CYP3A4 and P-glycoprotein by macrolides and ketolides may decrease the metabolic elimination of tolvaptan. Plasma concentrations and pharmacologic effects of tolvaptan may be increased by macrolides and ketolides.
Vasopressin antagonists (tolvaptan)	Nefazodone	Inhibition of CYP3A4 by nefazodone may decrease the metabolic elimination of tolvaptan. Plasma concentrations and pharmacologic effects of tolvaptan may be increased by nefazodone.

Generic Name	Interaction	Mechanism
Vasopressin antagonists (tolvaptan)	Moderate CYP3A4 Inhibitors	Inhibition of CYP3A isoenzymes by moderate CYP3A4 inhibitors may decrease the metabolic elimination of tolvaptan. Plasma concentrations and pharmacologic effects of tolvaptan may be increased by moderate CYP3A4 inhibitors.
Vasopressin antagonists (tolvaptan)	Rifamycins	Induction of CYP3A isoenzymes by rifamycins may increase the metabolic elimination of tolvaptan. Plasma concentrations and pharmacologic effects of tolvaptan may be decreased by rifamycins compromising therapeutic effectiveness.
Vasopressin antagonists (tolvaptan)	St. John's wort	Induction of CYP3A isoenzymes by St. John's wort may increase the metabolic elimination of tolvaptan. Plasma concentrations and pharmacologic effects of tolvaptan may be decreased by St. John's wort compromising therapeutic effectiveness.

CYP=cytochrome P450 isoenzymes, HIV=human immunodeficiency virus

VI. Adverse Drug Events

The most common adverse drug events reported with the vasopressin antagonists are listed in Table 6. The boxed warning for tolvaptan is listed in Table 7.

Table 6. Adverse Drug Events (%) Reported with the Vasopressin Antagonists[8]

Adverse Events	Tolvaptan
Cardiovascular	
Palpitations	4
Ventricular fibrillation	<2
Central Nervous System	
Cerebrovascular accident	<2
Dizziness	11
Fatigue	14
Pyrexia	4
Endocrine and Metabolic	
Diabetic ketoacidosis	<2
Hyperglycemia	6
Hypernatremia	≤4
Hyperuricemia	4
Gastrointestinal	
Abdominal distention	5
Anorexia	4
Constipation	7
Diarrhea	13
Dyspepsia	8
Ischemic colitis	<2
Nausea	21
Xerostomia	7 to 16
Genitourinary	
Pollakiuria	4 to 11
Polyuria	4 to 70
Urethral bleeding	<2
Vaginal hemorrhage	<2
Laboratory Abnormalities	
Bilirubin increased	<1
Increased serum alanine aminotransferase	5
Prothrombin time prolonged	<2
Musculoskeletal	
Rhabdomyolysis	<2

Adverse Events	Tolvaptan
Weakness	9
Respiratory	
Pulmonary embolism	<2
Respiratory failure	<2
Other	
Deep vein thrombosis	<2
Dehydration	2 to 3
Disseminated intravascular coagulation	<2
Hepatotoxicity	≤4
Hypersensitivity reaction	<1
Skin rash	4
Thirst	12 to 64
Xeroderma	5

✓ Percent not specified
- Event not reported

Table 7. Boxed Warning for Tolvaptan[2,4]

WARNING
Samsca® Initiate and re-initiate in a hospital and monitor serum sodium Samsca® should be initiated and re-initiated in patients only in a hospital where serum sodium can be monitored closely. • Too rapid correction of hyponatremia (e.g., >12 mEq/L/24 hours) can cause osmotic demyelination resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma and death. In susceptible patients, including those with severe malnutrition, alcoholism or advanced liver disease, slower rates of correction may be advisable. Not for use for autosomal dominant polycystic kidney disease (ADPKD) • Because of the risk of hepatotoxicity, tolvaptan should not be used for ADPKD outside of the FDA-approved REMS. **Jynarque®** • Jynarque® can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported. • Measure ALT, AST and bilirubin before initiating treatment, at two weeks and four weeks after initiation, then monthly for the first 18 months and every three months thereafter. Prompt action in response to laboratory abnormalities, signs, or symptoms indicative of hepatic injury can mitigate, but not eliminate, the risk of serious hepatotoxicity. • Because of the risks of serious liver injury, Jynarque® is available only through a restricted distribution program under a Risk Evaluation and Mitigation Strategy (REMS) called the Jynarque REMS Program.

VII. Dosing and Administration

The usual dosing regimens for the vasopressin antagonists are listed in Table 8.

Table 8. Usual Dosing Regimens for the Vasopressin Antagonists[2,4]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Tolvaptan	Hypervolemic and euvolemic hyponatremia: Tablet: initial, 15 mg once daily; maintenance, increase to 30 mg once daily after ≥24 hours as needed to achieve the desired level of serum sodium; maximum, 60 mg once daily Rapidly Progressing Autosomal Dominant Polycystic Kidney Disease	Safety and effectiveness have not been established in pediatric patients.	Tablet: 15 mg 30 mg 45 mg 60 mg 90 mg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	Tablet: initial, 60 mg orally per day as 45 mg taken on waking and 15 mg taken 8 hours later; Titrate to 60 mg plus 30 mg then to 90 mg plus 30 mg per day if tolerated with at least weekly intervals between titrations		

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the vasopressin antagonists are summarized in Table 9.

Table 9. Comparative Clinical Trials with the Vasopressin Antagonists

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Gheorghiade et al.[10] (2006) Tolvaptan 10 mg/day, with titration to larger doses (15, 30, 45, and 60 mg/day) as needed to achieve serum sodium concentrations within normal limits vs fluid restriction (initially 1,200 mL/24 hrs) plus placebo	AC, MC, OL, RCT Patients ≥18 years, serum sodium <135 mmol/L for ≥2 consecutive days, and normovolemia or signs of fluid overload	N=28 Inpatient treatment: 14 days Outpatient treatment: 14 days Follow-up: 65 days	Primary: Normalization of serum sodium concentration (defined as ≥135 mmol/L or an increase of >10% from baseline to the last inpatient assessment) Secondary: Changes in serum sodium from baseline to the last outpatient visit (day 65), urine osmolality, urine volume, urine sodium concentration, body weight, total fluid intake, thirst score from baseline to the last inpatient assessment	Primary: A higher proportion of subjects in the tolvaptan group had achieved the normalization of serum sodium compared to those in the fluid restriction group by the last inpatient visit (P=0.049). The normalization of serum sodium was achieved more rapidly in the tolvaptan group than in the fluid restriction group, occurring in 50% of tolvaptan-treated subjects by day four, compared to day eight in the fluid restriction group (P<0.03). Patients in the tolvaptan group had a significantly greater increase in serum sodium concentration 4 hours after the first dose (1.6 mmol/L; P=0.016), at day 5 (5.2 mmol/L; P=0.019) and at the last inpatient visit (5.7 mmol/L; P=0.0065) compared to patients receiving fluid restriction (-0.8, 0.7, and 1.0, respectively). Secondary: At day 65, the mean change in serum sodium was 4.7 mmol/L in the tolvaptan group compared to -0.3 mmol/L in the placebo group (P=0.039). Urine sodium was significantly lower (P=0.021) and urine output was significantly greater (P=0.014) in the tolvaptan group compared to the placebo group. No significant differences in urine osmolality (P=0.058), serum potassium (P=0.45), blood pressure, heart rate, body weight (P value not significant), thirst score (P=0.8) or adverse events requiring drug discontinuation were observed between the treatment groups.
Schrier et al.[11] (2006) SALT-1 and SALT-2 Tolvaptan 15	DB, MC, PC, RCT Patients ≥18 years of age with euvolemic or hypervolemic	N=102 (SALT-1) N=123 (SALT-2)	Primary: Change in the average daily AUC for the serum sodium from baseline to day 4	Primary: By day four, the increase in the average daily AUC for the serum sodium concentration was 3.62 and 4.33 for tolvaptan (SALT-1 and SALT-2, respectively) compared to 0.25 and 0.42 for placebo (P<0.001 for all comparisons).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day for 30 days (dose could be titrated to 60 mg/day) vs placebo	hyponatremia (serum sodium <135 mmol/L). Patients also had chronic heart failure, cirrhosis, or the syndrome of inappropriate antidiuretic hormone secretion (SIADH) in association with the hyponatremia.	37 days	and from baseline to day 30 Secondary: Change in the AUC for the serum sodium in patients with marked hyponatremia, serum sodium concentration at each visit, time to normalization of the serum sodium, percent of patients with serum sodium concentrations that normalized at day 4 and day 30, serum sodium concentration on day 4 and day 30 for patients with mild or marked hyponatremia at baseline, change from baseline in scores on the Physical Component Summary and Mental component summary of the medical outcomes Study 12-item Short-Form General Health	By day 30, the increase in the average daily AUC for the serum sodium concentration was 6.22 and 6.20 for tolvaptan (SALT-1 and SALT-2, respectively) compared to 1.66 and 1.84 for placebo (P<0.001 for all comparisons). Secondary: By day 30, the increase in the average daily AUC for the serum sodium concentration in patients with marked hyponatremia was 8.24 and 7.60 for tolvaptan (SALT-1 and SALT-2, respectively) compared to 2.54 and 2.72 for placebo (P<0.001 for all comparisons). By day four, serum sodium concentrations were 133.9 and 135.3 mmol/L for tolvaptan (SALT-1 and SALT-2, respectively) compared to 129.7 and 129.6 mmol/L for placebo (P<0.001 for all comparisons). By day 30, serum sodium concentrations were 135.7 and 135.9 mmol/L for tolvaptan (SALT-1 and SALT-2, respectively) compared to 131 and 131.5 mmol/L for placebo (P<0.001 for all comparisons). By day four, 40 and 55% of patients receiving tolvaptan (SALT-1 and SALT-2, respectively) had normal serum sodium concentrations compared to 13 and 11% for placebo (P<0.001 for all comparisons). By day 30, 53 and 58% of patients receiving tolvaptan (SALT-1 and SALT-2, respectively) had normal serum sodium concentrations compared to 25 and 25% for placebo (P<0.001 for all comparisons). Scores on the Physical Component Summary did not differ significantly between groups. Scores for the Mental Component Summary improved in the tolvaptan group when the data from SALT-1 and SALT-2 were combined (P=0.02), as well as in SALT-1 (P=0.04). Scores improved significantly in the combined subgroup of patients with marked hyponatremia (P=0.04). There was no significant difference between the groups found in SALT-2 (P=0.14). Adverse event profiles in the two study groups were similar for all comparisons. The most common adverse events occurring during the study in the tolvaptan groups were thirst and dry mouth. Overall, there were 26 serious adverse events potentially related to the study treatment in SALT-1

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Survey	and SALT-2. The number of deaths in the two study groups was similar (14 deaths among 223 patients in the tolvaptan groups and 13 deaths among 220 patients in the placebo groups), and they occurred within the defined observation period. In four of the patients in the tolvaptan group, the desirable rates of sodium correction were exceeded during the first 24 hours of the study (>0.5 mmol/L per hour). In four patients (1.8%), the predefined serum sodium concentration (>146 mmol per liter) was exceeded.
Berl et al.[12] (2010) SALTWATER Tolvaptan QD (dose varied based on response)	OL, ES (Extension of SALT-1 and SALT-2) Patients ≥18 years of age with euvolemic or hypervolemic hyponatremia (serum sodium <135 mmol/L). Patients also had chronic heart failure, cirrhosis, or the SIADH in association with the hyponatremia	N=111 4 years (mean 1.9 years)	Primary: Safety, efficacy Secondary: Not reported	Primary: During the follow-up period, 105 of 111 patients experienced an adverse event. The most common adverse events that were potentially related to tolvaptan use were pollakiuria, thirst, fatigue, dry mouth, polydipsia, polyuria, hypotension, hypernatremia, dizziness, headache, peripheral edema, and acute renal failure. A total of 19 patients died during the follow-up period (9 deaths per 100 patient-years of exposure). The death rate during SALTWATER was lower than that observed for SALT (86.9 deaths per 100 patient-years of exposure). In five patients, serum sodium correction exceeded the rate of 1 mmol/L per h at the eight hour time point. There were 18 patients who had serum sodium levels >145 mmol/L at individual time points. Correction of serum sodium levels during the first eight hours of therapy occurred at similar rates in SALTWATER compared to SALT-1 and SALT-2. After the initial titration period, mean serum sodium levels remained within the normal range throughout the four year treatment period. In all patient subgroups, serum sodium levels declined by seven days of withholding tolvaptan. On drug discontinuation, the proportion of patients who declined by ≥3 mEq/L was 68%, and an equal proportion fell from ≥135mEq/L to below this threshold of normal. The mean time to first fluid restriction was 122.3 and 162.5 days in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				mild and marked hyponatremia subgroups, respectively; 13.2% of patients in the mild hyponatremia group and 5.4% in the marked hyponatremia group required fluid restriction. Secondary: Not reported
Cardenas et al. (abstract)[13] (2012) SALT-1 and SALT-2 Tolvaptan 15 mg/day for 30 days (dose could be titrated to 60 mg/day) vs placebo	Subgroup analysis Patients with cirrhosis and hyponatremia	N=120 30 days	Primary: Change in the average daily AUC for the serum sodium from baseline to day 4 and from baseline to day 30 Secondary: Mental component summary of the medical outcomes Study 12-item Short-Form General Health Survey, safety	Primary: Treatment with tolvaptan effectively raised serum sodium. Average daily AUC for serum sodium was significantly greater with tolvaptan from baseline to day 4 (P<0.0001) and day 30 (P<0.0001) compared to placebo. Superiority of tolvaptan was maintained after stratification by baseline hyponatremia (mild and marked), eGFR (≤60 and >60 mL/min), or serum creatinine levels (<1.5 and ≥1.5 mg/dL). Hyponatremia recurred seven days after discontinuation of tolvaptan. Secondary: Mean mental component summary scores of the Short-Form General Health Survey improved from baseline to day 30 with tolvaptan but not with placebo (4.68 vs 0.08; P=0.02). Major adverse events with tolvaptan were dry mouth and thirst. Gastrointestinal bleeding occurred in 10 and 2% of patients receiving tolvaptan and placebo, respectively (P=0.11). Rates of adverse events, withdrawals, and deaths were similar with both treatments.
Udelson et al.[14] (2008) Tolvaptan 15, 30, or 60 mg administered as a single dose vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with symptomatic heart failure (NYHA class III or IV) of ≥3 months' duration caused by LVEF <40%. Patients were also required to be on standard	N=181 12 hours	Primary: PCWP peak change from baseline within 3 to 8 h after treatment administration Secondary: AUC for the change from baseline PCWP	Primary: The pairwise comparisons of 15, 30, and 60 mg tolvaptan versus placebo each showed a statistically significant decrease in peak change in PCWP from three to eight hours post-dose (P=0.003, P=0.044, and P=0.033, respectively). Secondary: For the $AUC_{0\text{-}8h}$, the 15 mg tolvaptan group was the only tolvaptan dose group that was statistically significantly different from placebo. All tolvaptan doses produced statistically significantly greater changes than placebo in peak change in pulmonary artery pressure (P<0.01 for 15

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	background therapy for heart failure for ≥1 month.		and other hemodynamic parameters over an 8 hour evaluation period and renal and electrolyte parameters	mg; P<0.05 for 30 and 60 mg). Tolvaptan 15 and 30 mg doses resulted in statistically significant reductions in peak change in right atrial pressure as compared to placebo (P<0.01 and P<0.05, respectively). No significant changes in cardiac index, pulmonary vascular resistance, and systemic vascular resistance were observed after tolvaptan administration compared to placebo. The single dose of tolvaptan produced a dose-dependent increase in urine output (P<0.0001 for all tolvaptan groups vs placebo). Urine osmolality was significantly reduced by all doses of tolvaptan relative to placebo (P<0.0001 for all tolvaptan groups vs placebo). Free water clearance was significantly greater for all tolvaptan doses relative to placebo at all time points. Plasma osmolality increased in all of the tolvaptan-treated groups compared to placebo. Serum sodium levels showed a dose-related increase compared to placebo (1.2, 3.3, 4.6, and -0.7 mEq/L for the tolvaptan 15, 30, 60 mg, and placebo groups, respectively). Potassium levels were not different from placebo in any of the tolvaptan dosing groups. No significant changes in serum creatinine, blood urea nitrogen, serum potassium, and vital signs were observed after study drug administration. Tolvaptan was well tolerated relative to placebo. Patient-reported adverse events in this short-term study occurred in 45.5, 44.2, 54.3, and 33.3% of the 15, 30, and 60 mg tolvaptan and placebo groups, respectively.
Udelson et al.[15] (2007) Tolvaptan 30 mg/day vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with CHF (NYHA class II to III) with a LVEF <30%. Patients were also required to be on standard background therapy for heart failure for	N=240 55 weeks	Primary: Change from baseline in LVEDV index Secondary: Change from baseline in LVESV index, comparison of the change from baseline in	Primary: In the placebo group, there was no change in LVEDV index over the year of follow-up. After one year of tolvaptan therapy, there was a small reduction in LVEDV index; however, this was not significantly different from placebo (-1.8 mL/m^2; P=0.21 vs placebo). There was also no difference in the change of volumes from baseline at the week 55 study. Secondary: In the placebo group, LVEDV index decreased 0.4 mL/m^2 compared to a decrease of 3.3 mL/m^2 in the tolvaptan group (P=0.09). There was no difference in the change of LVESV index from baseline at week 55.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	≥3 months before enrollment.		LVEDV index after drug withdrawal (week 55), assessment of symptoms (using subject-assessed symptom scales and the Minnesota Living With Heart Failure Questionnaire)	Ejection fraction changes were small and similar in both treatment groups. Only minor changes in blood pressure and heart rate were observed over the course of the trial; there were no significant differences in the tolvaptan versus placebo groups. There were no significant between-group differences in serum sodium or potassium across the course of the trial. There were also no differences in renal function parameters (BUN and serum creatinine) across the year of therapy. No statistically significant differences were observed between the tolvaptan group and the placebo group for the change from baseline in Minnesota Living With Heart Failure Questionnaire score or for the Visual Analog Scale assessment of global status or respiratory status. More subjects in the tolvaptan group reported a score of "better" in the subject-assessed overall treatment effect at each visit than did subjects in the placebo group; however, no statistically significant differences were observed between treatment groups. There were six deaths (5%) and 21 hospitalizations of patients with heart failure (18%) in the tolvaptan-treated group, compared to 11 deaths (9%) and 34 heart failure hospitalizations (28%) in the placebo-treated group (P<0.03 for the composite of death and heart failure hospitalizations). Adverse events including urinary frequency, thirst, and dry mouth occurred more frequently with tolvaptan than with placebo therapy. There was no difference in the number of patients withdrawn from the trial as the result of bothersome side effects between the two randomization groups.
Gheorghiade et al.[16] (2007) EVEREST Tolvaptan 30 mg/day within 48 hours of admission vs	DB, MC, PC, RCT Patients ≥18 years of age with a history of chronic heart failure who had been hospitalized for worsening CHF and who had a LVEF ≤40%.	N=2,048 (Trial A) N=2,085 (Trial B) 7 days	Primary: Composite score of changes from baseline in patient-assessed global clinical status and body weight at day 7 or discharge	Primary: The composite score of changes from baseline in patient-assessed global clinical status and body weight at day seven or discharge was greater with tolvaptan compared to placebo (Trial A, mean 16 vs 0.99; P<0.001; Trial B, mean 17 vs 0.97; P<0.001). Improvement in patient-assessed global clinical status (assessed alone), measured by a 100-point visual analog scale at day seven or discharge, was similar between the tolvaptan and placebo groups (Trial A, mean 18.25 vs 17.73; P=0.51; Trial B, mean 18.72 vs 18.28; P=0.52).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	Patients also received conventional heart failure therapy.		Secondary: Patient-assessed changes in dyspnea at day 1, global clinical status at day 7 or discharge, body weight at days 1 and 7 or discharge, and peripheral edema at day 7 or discharge	Mean body weight reductions at day seven or discharge in the tolvaptan and placebo groups were 3.35 vs 2.73 kg, respectively, in Trial A (P<0.001) and 3.77 vs 2.79 kg, respectively, in Trial B (P<0.001). Secondary: More patients in the tolvaptan groups (76.74% in Trial A and 72.06% in Trial B) reported an improvement dyspnea at day one (for those patients with dyspnea at baseline) compared to placebo (70.61% in Trial A and 65.32% in Trial B; P<0.001 in both Trials). There was no significant difference in global clinical status at day seven or discharge between the tolvaptan or placebo treatment groups (Trial A, P=0.51; Trial B, P=0.52). Changes in mean body weight were significantly greater with tolvaptan at day one (Trial A, -1.71 kg; Trial B -1.82 kg) than with placebo (Trial A, -0.99 kg; Trial B, 0.95 kg; P<0.001 in both trials). There was no difference in peripheral edema at inpatient day seven or discharge with tolvaptan vs placebo in Trial A. In Trial B, 73.67% of patients experienced at least a 2-grade improvement in pedal edema with tolvaptan compared to placebo (P=0.02). An overall in-hospital mortality rate of 2.4 and 2.9% was observed in the tolvaptan and placebo groups, respectively. Through day seven or discharge, adverse events were reported in 49.1 and 40.0% of patients in Trial A, and in 55.9 and 47.9% of patients in Trial B in the tolvaptan and placebo groups, respectively.
Konstam et al.[17] (2007) EVEREST Tolvaptan 30 mg/day within 48 hours of admission	DB, MC, PC, RCT Patients ≥18 years of age with a history of chronic heart failure who had been hospitalized for worsening CHF	N=4,133 ≥60 days	Primary: All-cause mortality, composite of cardiovascular death or hospitalization for heart failure	Primary: The median duration of follow-up was 9.9 months. A total of 537 patients in the tolvaptan group (25.9%) and 543 patients in the placebo group (26.3%) died (HR, 0.98; 95% CI, 0.87 to 1.11; P=0.68). A total of 871 patients in the tolvaptan group (42.0%) and 829 patients in the placebo group (40.2%) died from cardiovascular causes or had a first hospitalization for heart failure (HR, 14; 95% CI, 0.95 to 1.14; P=0.55).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	and who had a LVEF ≤40%. Patients also received conventional heart failure therapy.		Secondary: Composite of cardiovascular mortality or cardiovascular hospitalization, incidence of cardiovascular mortality, incidence of clinical worsening of heart failure (death, hospitalization for heart failure, or unscheduled visit for heart failure), changes from baseline in body weight at day 1, serum sodium level at day 7 or discharge, edema score at day 7 or discharge, patient-assessed dyspnea at day 1, and Kansas City Cardiomyopathy Questionnaire overall summary score at outpatient week 1	Secondary: The composite of cardiovascular death or cardiovascular hospitalization, the incidence of cardiovascular mortality, and the incidence of clinical worsening of heart failure did not differ between the two treatment groups (P=0.52, P=0.67 and P=0.62, respectively). In patients with dyspnea at baseline, patient-assessed dyspnea scores significantly improved at day one in patients receiving tolvaptan compared to placebo (P<0.001), with 74.3% of the tolvaptan group and 68.0% of the placebo group demonstrating an improvement in dyspnea score. Mean body weight at day one was reduced by 1.76 kg in the tolvaptan group and by 0.97 kg in the placebo group (P<0.001). Among patients with baseline serum sodium levels less than 134 mEq/L, mean serum sodium concentrations increased by 5.49 mEq/L at day 7 or discharge with tolvaptan compared to 1.85 mEq/L in the placebo group (P<0.001). This effect was observed as early as day one and was maintained through 40 weeks of treatment. In patients with baseline pedal edema, edema scores significantly improved at day seven or discharge in patients receiving tolvaptan compared to placebo (P=0.003), with 73.8% of tolvaptan patients and 70.5% of placebo patients manifesting improvement in edema by at least two grades. A significant improvement in physician-assessed pedal edema was observed as early as day one and continued through post-discharge week four. No significant changes were observed at outpatient week one in the Kansas City Cardiomyopathy Questionnaire overall summary score. Statistically significant changes favoring tolvaptan were observed at the time of the last scheduled on-treatment assessment at study end for the quality-of life domain (P=0.003), the social limitation domain (P=0.05), and the overall summary score (P=0.02). The other domains (clinical summary, physical limitation, total symptom, symptom frequency,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				symptom burden, symptom stability, and self-efficacy) did not reach significance at the time of the last on-treatment assessment. Adverse events occurred in 89.0% of tolvaptan patients and 86.1% of placebo patients.
Pang et al.[18] (2009) EVEREST Tolvaptan 30 mg/day within 48 hours of admission vs placebo	Post-hoc analysis of EVEREST Patients ≥18 years of age with a history of chronic heart failure who had been hospitalized for worsening CHF with LVEF ≤40%. Patients also received conventional heart failure therapy.	N=3,664 1 to 3 days	Primary: Patient-assessed dyspnea using a seven-point Likert scale administered on day 1 after randomization Secondary: Not reported	Primary: Tolvaptan was associated with improved patient-assessed dyspnea on inpatient day one compared to placebo (74.3 vs 68.0%; P<0.0001) as reported in the primary EVEREST analysis. The greatest treatment differences were seen in subjects with continuous dyspnea at baseline. Patients were divided post hoc into five groups, based on time (in hours) of dyspnea assessment after the first dose of tolvaptan. The percentage improvement with placebo stayed relatively constant, whereas improvement with tolvaptan was greatest when measured early (P<0.05). The majority of patients had an improvement in dyspnea at all time points relative to hospital admission; however, there was a significantly higher rate of improvement with tolvaptan compared to placebo (P<0.05). There was also a linear association between reductions in body weight and improvements in patient-assessed dyspnea. Secondary: Not reported
Hauptman et al.[19] (2013) EVEREST Tolvaptan 30 mg/day within 48 hours of admission vs placebo	Post-hoc analysis of EVEREST Patients ≥18 years of age with a history of chronic heart failure who had been hospitalized for worsening CHF with LVEF ≤40%. Patients also received conventional heart	N=475 ≥60 days	Primary: Body weight at day 1, serum sodium at day 7 or discharge in patients with a baseline serum sodium <135 mEq/L, edema score at day 7 or discharge for those with peripheral edema at baseline, dyspnea at day 1	Primary: Mean change from baseline in serum sodium was 4.72 mEq/L vs 1.18 mEq/L at day one and 4.90 mEq/L vs 1.93 mEq/L at day seven in the tolvaptan and placebo groups, respectively (P<0.0001 at each time point). Tolvaptan was more likely to lead to normalization of serum sodium defined by a value of ≥135 mEq/L at both day one and at discharge compared with placebo (58 vs 20% and 64 vs 29%, respectively; P<0.001 for both comparisons). In patients with dyspnea and hyponatremia at baseline (n=409), the changes in dyspnea were more favorable in the tolvaptan group versus placebo (van Elteren analysis: 0.56, 95% CI 0.51 to 0.62; P=0.028).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	failure therapy. This analysis included the hyponatremic cohort.		for those with dyspnea at baseline, long-term clinical course Secondary: Not reported	Mean body weight at day one was reduced by 1.69 kg in the tolvaptan group and by 0.96 kg in the placebo group (P<0.0001). Changes observed in physician-assessed edema at day seven (or discharge if earlier) were not significantly different between the groups (P=0.79). Serum sodium increases observed in the short term among the patients with hyponatremia continued during the outpatient portion of the study, with results significantly favoring tolvaptan. There was a favorable effect of tolvaptan treatment on first occurrence of cardiovascular mortality or morbidity in those with more severe reduction in serum sodium at baseline (HR, 0.60; 95% CI, 0.37 to 0.98; P=0.04). There was no effect of tolvaptan on CV mortality or morbidity in the mild hyponatremia group, with baseline serum sodium 130 to 134 mEq/L (HR, 0.96; 95% CI, 0.74 to 1.25; P=0.77). Secondary: Not reported
Gheorghiade et al.[20] (2004) ACTIV IN CHF Tolvaptan 30, 60, or 90 mg/day vs placebo	DB, MC, PC, RCT Patients ≥18 years of age admitted for worsening CHF with LVEF <40% within 1 year of admission and systemic congestion (JVD, rales, or peripheral edema after initial in-hospital therapy for heart failure). Patients also received conventional heart failure therapy.	N=319 Inpatient: 10 days Outpatient: 7 weeks	Primary: Change in body weight at 24 hrs after the administration of the first dose of study drug; worsening heart failure at 60 days Secondary: Changes in dyspnea, JVD, rales, edema, body weight, urine output, serum electrolyte levels, length of hospital stay after	<u>Inpatient Phase</u> Primary: A greater median reduction in body weight was found in patients treated with tolvaptan compared to placebo 24 hrs after the administration of the first dose of study drug (-1.80, -2.10, -2.05, and -0.60 kg for tolvaptan 30, 60, and 90 mg, and placebo, respectively; P=0.002, P=0.002, and P=0.009 for the 3 tolvaptan groups compared to the placebo group). Secondary: The median body weight reductions from baseline to discharge were greater in the tolvaptan groups compared to the placebo group (-3.30, -2.80, -3.20, and -1.90 kg in the groups receiving tolvaptan 30, 60, and 90 mg, and placebo, respectively; P=0.006, P=0.002, and P=0.06 for the three tolvaptan groups compared to placebo). The mean urine output at 24 hrs was 4,056.2, 4,175.2, 4,127.3, and 2,296.5 mL for the tolvaptan 30, 60, and 90 mg, and placebo groups, respectively (P =0.02, P<0.001, and P<0.001 for the three tolvaptan groups compared to the placebo group).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			randomization, use of diuretics, and patient/physician-assessed symptom scales	Signs and symptoms of heart failure improved in all patients during the period of hospitalization. There were no significant differences in JVD, and peripheral edema between the treatment groups (dyspnea P=0.04). Global assessment scales did not show a significant difference among the treatment groups. The median length of time between randomization and discharge was 4 days in both treatment groups. <u>Outpatient Phase</u> Primary: There was no significant difference in worsening heart failure between the tolvaptan groups and the placebo group. Secondary: Diuretic use decreased in all patients after discharge. There was no significant difference in mean dose reduction between the treatment groups.
Gheorghiade et al.[21] (2003) Tolvaptan 30, 45, or 60 mg/day vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with a diagnosis of CHF irrespective of LVEF. Patients also received conventional heart failure therapy.	N=254 25 days	Primary: Changes in body weight Secondary: Ankle edema measurements, urine sodium excretion, urine volume, urine osmolality, safety	Primary: Mean decreases from baseline in body weight were observed on the first day of tolvaptan treatment at all doses and maintained throughout the study (P<0.001 vs placebo). The decrease in body weight was similar in all tolvaptan-treated patients irrespective of the LVEF. Patients receiving placebo experienced an increase in body weight from baseline. Secondary: Improvements in ankle edema scores were significantly better with tolvaptan 45 mg compared to placebo (P<0.05). None of the other doses studies differed significantly from placebo. Tolvaptan-treated patients had significantly greater mean total urinary sodium excretions (339.9, 373.0, and 355 mEq for the 30, 45, and 60 mg tolvaptan groups, respectively) than placebo-treated patients (193.7 mEq; P<0.05). Urine volumes were greater in tolvaptan-treated patients (3,909, 4,232,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				and 4,597 mL for the 30, 45, and 60 mg tolvaptan groups, respectively) than in placebo-treated patients (2,328 mL; P<0.05). At day one, urine osmolality decreased by 15.5, 52.4, and 118.8 mOsm/kg in the 30, 45, and 60 mg tolvaptan groups, respectively compared to an increase of 135.8 mOsm/kg in the placebo group (P<0.05 for all comparisons). No significant differences were found between the tolvaptan groups and the placebo group in the QOL assessment. No changes in heart rate or systolic or diastolic blood pressure, supine or standing, were observed in the tolvaptan groups during the study. Dry mouth, thirst, and polyuria, including urinary frequency, were higher in the tolvaptan-treated patients.
Salahudeen et al.[22] (2014) Tolvaptan vs placebo Both groups received the standard of care for hyponatremia, except that patients were allowed to drink to thirst	DB, RCT Adult patients with cancer who were admitted to MD Anderson and met the eligibility criteria for nonhypovolemic hyponatremia (125 to 130 mmol/L serum sodium)	N=30 14 days	Primary: To compare the rate of tolvaptan-treated correction of hyponatremia with that of placebo on day 14 Secondary: To compare the length of hospital stay and the change in mental test scores between the tolvaptan-treated and placebo groups	Primary: Sixteen of 17 patients in the tolvaptan group and one of 13 patients in the placebo group achieved the primary endpoint of serum sodium correction on day 14 (94 vs 8%, respectively; P<0.001). The study met the predefined stopping rule of superiority for tolvaptan over placebo and further patient recruitment was halted. Secondary: The secondary endpoints between the tolvaptan and placebo groups (mean ± standard deviation) for length of stay (21 ± 15 vs 26 ± 15 days, respectively) and changes in the MMSE score (−0.35 ± 1.66 vs 0.31 ± 2.42, respectively) were not significantly different.
Dahl et al.[23] (2012) Vaptans (tolvaptan,	MA (12 RCTs) Patients with cirrhosis and hyponatremia or	N=2,266 Duration not specified	Primary: Mortality Secondary: Complications to	Primary: No clear difference between vaptans and control was found regarding mortality (22 vs 20%; RR, 1.06; 95% CI, 0.90 to 1.26). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
satavaptan*, lixivaptan*) vs control (no intervention, placebo, other diuretics)	ascites		cirrhosis (variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis, and hepatorenal syndrome), renal failure, serum sodium levels, mobilization of ascites, safety	No clear differences between vaptans and control were found regarding complications to cirrhosis and renal failure. Treatment with vaptans increased serum sodium levels (WMD, 1.8 mmol/L; 95% CI, 0.79 to 2.96). Treatment with vaptans reduced weight (WMD, -1.82 kg; 95% CI, -2.86 to 0.79), time to first paracentesis (RR, 0.76; 95% CI, 0.63 to 0.90), and the clinical severity of ascites (RR, 0.71; 95% CI, 0.60 to 0.83). Adverse events were more likely with vaptan therapy compared to control (RR, 3.97; 95% CI, 1.78 to 8.83), including an excessive urine volume (RR, 9.96; 95% CI, 1.38 to 71.68). Treatment with vaptans had no effect on SBP and DBP. Treatment with vaptans increased vasopressin and renin levels; however, there is no clear difference between treatments in aldosterone levels.
Torres et al.[24] (2011) TEMPO 3:4 Tolvaptan 45, 60, or 90 mg QAM and 15 or 30 mg QPM vs placebo	DB, MC, RCT Adults 18 to 50 years of age with ADPKD, total kidney volume (TKV) ≥750 mL, CrCl ≥ 60 mL/min	N=1,445 36 months	Primary: Annual rate of percentage change in TKV Secondary: ADPKD progression as measured by worsening kidney function, significant kidney pain, worsening hypertension, and worsening albuminuria	Primary: Over the three-year period, total kidney volume increased by 2.8% per year (95% CI, 2.5 to 3.1) with tolvaptan versus 5.5% per year (95% CI, 5.1 to 6.0) with placebo. Tolvaptan changed the rate of growth by −2.7 percentage points per year (95% CI, −3.3 to −2.1); the ratio of the geometric means of growth rate was 0.97 (95% CI, 0.97 to 0.98; P<0.001). Tolvaptan changed the rate of growth by -2.7 percentage points per year and a mixed-model repeated-measures analysis confirmed the analysis noting percent change of 9.65% with tolvaptan vs 18.85% with placebo; a difference of -9.2 percentage points (95% CI, -11.1 to -7.3; P<0.001). Secondary: The relative rate of ADPKD-related events was decreased by 13.5% in tolvaptan treated patients as compared with placebo (44 vs 50 events per 100 person-years (HR, 0.87; 95% CI, 0.78 to 0.97; P<0.01). Effects on worsening kidney function and kidney pain events drove the result of secondary endpoint. Tolvaptan exhibited no effect on hypertension or albuminuria events.
Raina et al.[25] (2021) TEMPO 3:4	Post-hoc analysis of TEMPO 3:4	N=1,445 36 months	Primary: Annual rate of change in TKV	Primary: Over the three year period, TKV in the adolescents and young adults group treated with tolvaptan increased by 3.8% per year (95% CI, 3.8 to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tolvaptan 45, 60, or 90 mg QAM and 15 or 30 mg QPM vs placebo	Adults 18 to 50 years of age with ADPKD, total kidney volume (TKV) ≥750 mL, CrCl ≥ 60 mL/min		after three years in patients aged 18 to 24 years Secondary: Long-term safety of tolvaptan in patients 18 to 24 years of age by assessing the number of patients who had liver toxicity as defined per Hy's law	5.2) compared to 6.5% per year (95% CI, 4.2 to 8.6) with placebo. Tolvaptan decreased the rate of growth by 2.7 percentage points per year (P=0.0491) compared to placebo and represents a treatment effect of 41.2%. Secondary: In both the AYA and adult groups, none of the patients met the criteria for Hy's law of hepatotoxicity.
Torres et al.[26] (2017) REPRISE Tolvaptan 45, 60, or 90 mg QAM and 15 or 30 mg QPM vs placebo	DB, MC, RCT Adults 18 to 55 years of age with ADPKD with eGFR 25 to 65 mL/min or 56 to 65 years of age with eGFR 25 to 44 mL/min	N=1,370 12 months	Primary: Annualized mean change in eGFR from pre-treatment baseline to post-treatment follow-up Secondary: Mean change in annualized eGFR slope	Primary: The change from baseline in the eGFR was −2.34 ml/min (95% CI, −2.81 to −1.87) in the tolvaptan group, as compared with −3.61 ml/min (95% CI, −4.08 to −3.14) in the placebo group (difference, 1.27 ml/min; 95% CI, 0.86 to 1.68; P<0.001). Secondary: The difference in mean change in annualized eGFR slope between tolvaptan and placebo was 1.01 mL/min (95% CI, 0.62 to 1.40; P<0.001).

*Drug not available in the United States.
Drug regimen abbreviations: QD
Study design abbreviations: AC=active comparator, DB=double blind, ES=extended study, MA=meta analysis, MC=multicenter, OL=open label, PC=placebo controlled, RCT=randomized controlled trial
Miscellaneous abbreviations: ADPKD=autosomal dominant polycystic kidney disease, AUC=area under the curve, CHF=congestive heart failure, CI=confidence interval, DBP=diastolic blood pressure, eGFR=estimated glomerular filtration rate, HR=hazard ratio, JVD=jugular venous distention, LVEDV=left ventricular end diastolic volume, LVEF=left ventricular ejection fraction, LVESV=left ventricular end systolic volume, PCWP=pulmonary capillary wedge pressure, QOL=quality of life, RR=relative risk, SBP=systolic blood pressure, SIADH=syndrome of inappropriate antidiuretic hormone secretion, WMD=weighted mean difference

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 10. Relative Cost of the Vasopressin Antagonists

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Tolvaptan	tablet	Jynarque®, Samsca®*	$$$$$	$$$$$

N/A=not available

X. Conclusions

Tolvaptan (Samsca®) is FDA-approved for the treatment of clinically significant euvolemic and hypervolemic hyponatremia (serum sodium <125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure and SIADH.[2] The management of hyponatremia depends on the clinical presentation and duration of the disease. Treatment must be approached carefully as overly rapid correction of hyponatremia (>10 to 12 mEq/L per 24 hours) may cause osmotic demyelination.[2,3,6]

There are limited guidelines available that discuss the management of hyponatremia. An expert panel provided treatment recommendations in 2013, which includes fluid restriction, sodium chloride administration, and diuresis. The panel concluded that the current role for vasopressin antagonists in SIADH is in treating mild to moderate hyponatremia and asymptomatic severe hyponatremia. Because there is a paucity of data for patients with severely symptomatic hyponatremia, hypertonic saline remains the treatment of choice in this group until more evidence-based data are available. In patients with heart failure, a vasopressin antagonist is recommended if

serum sodium does not correct to the desired level with hypertonic saline or fluid restriction. The fluid restriction should be lifted before starting these agents.[3]

Three short-term trials evaluating the safety and efficacy of tolvaptan in a relatively small number of patients with euvolemic or hypervolemic hyponatremia demonstrated significant improvements in serum sodium concentrations compared to fluid restriction or placebo.[10,11] An open-label, long-term extension study (mean follow-up of 701 days) assessed the drug-related adverse effects of tolvaptan and maintenance of efficacy, and concluded that prolonged administration of tolvaptan maintained an increased serum sodium level with an acceptable margin of safety.[12] Evidence suggests that hyponatremia recurs after discontinuation of tolvaptan.[12,13] Several other studies have evaluated the use of tolvaptan in patients with congestive heart failure as an add-on to conventional treatments.[14-17,19,21,22] Significant changes in body weight have been observed; however, the long-term use of tolvaptan (median duration 9.9 months) failed to demonstrate any improvements in mortality or hospitalizations for worsening heart failure.[17] A meta-analysis also failed to demonstrate a benefit in mortality with vaptan therapy compared to control in patients with cirrhosis and hyponatremia or ascites.[23]

Data supporting the use of tolvaptan are limited. It has not been established that raising serum sodium with tolvaptan provides a symptomatic benefit to patients. Patients requiring intervention to raise serum sodium urgently should not be treated with tolvaptan. Hospitalization is required for initiation and reinitiation of tolvaptan therapy so that serum sodium can be monitored closely.[2]

Tolvaptan is now also available under the brand name Jynarque®, which is indicated to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD).[4] Safety and efficacy were established in two phase III trials, treating almost 3,000 adult patients with early and late stage ADPKD. Tolvaptan slowed the increase in total kidney volume and decreased ADPKD-related events, including deterioration of kidney function and pain, as compared to placebo.[24,25] Guidelines for the use of tolvaptan in ADPKD are limited, but the Updated Canadian Expert Consensus on Assessing Risk of Disease Progression and Pharmacological Management of Autosomal Dominant Polycystic Kidney Disease does suggest using tolvaptan in line with the FDA-approved indication.[9]

There is insufficient evidence to conclude that tolvaptan offers a significant clinical advantage over other alternatives in general use. Since tolvaptan is not indicated as first-line therapy for the management of hyponatremia, it should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand vasopressin antagonists within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand vasopressin antagonist is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Diuretics, Miscellaneous
AHFS Class 402892
May 8, 2024

I. Overview

In July 2010, conivaptan and tolvaptan were moved from the miscellaneous diuretics class (AHFS Class 402892) to the vasopressin antagonists class (AHFS Class 402828). Currently, there are no drugs classified by AHFS as miscellaneous diuretics.

II. Conclusions

There are no drugs available in the miscellaneous diuretics class (AHFS Class 402892).

III. Recommendations

No brand miscellaneous diuretic is recommended for preferred status. Alabama Medicaid should continue to include AHFS Class 402892 in the PDL screening process. If new outpatient miscellaneous diuretics are added, it is recommended that this class be re-reviewed at that time.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Alzheimer's Agents
Parasympathomimetic (Cholinergic) Agents, AHFS Class 120400
Central Nervous System Agents, Miscellaneous, AHFS Class 289200
May 8, 2024

I. Overview

Alzheimer's disease is a progressive neurodegenerative disorder in older adults that affects cognition, behavior, and activities of daily living.[1,2] It is the most common form of dementia and the average life expectancy from the onset of symptoms to death is approximately 10 years.[1-3] Diagnostic features include memory impairment and one or more of the following: aphasia, apraxia, agnosia, and/or disturbance in executive functioning.[1]

The pathophysiologic mechanisms are not entirely understood; however, the disease is characterized by the accumulation of intracellular neurofibrillary tangles and extracellular amyloid plaques in various regions of the brain. Inflammation and free radical processes lead to neuron dysfunction and death. It is thought that memory loss is partially the result of a deficiency of cholinergic neurotransmission.[2-3] Glutamate, an excitatory neurotransmitter, may also play a role in the pathophysiology of Alzheimer's disease. Glutamate activates N-methyl-D-aspartate (NMDA) receptors and is involved in learning and memory. However, excessive amounts of glutamate in the brain may lead to excitotoxicity and cell death.[3]

Agents approved for the treatment of dementia of Alzheimer's disease include cholinesterase inhibitors (donepezil, galantamine, and rivastigmine), an NMDA receptor antagonist (memantine), and a combination product (memantine-donepezil).[4-11] Although none of the agents delay the progression of neurodegeneration, they do delay the progression of symptoms. The cholinesterase inhibitors enhance cholinergic function by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by acetylcholinesterase. Memantine blocks NMDA receptors and inhibits their overstimulation by glutamate. The combination product containing memantine and donepezil (Namzaric®) was launched in May 2015 with the indication for the treatment of moderate to severe dementia of the Alzheimer's type in patients stabilized on 10 mg of donepezil hydrochloride once daily.[11]

Aducanumab-avwa is the first disease modifying therapy approved for the treatment of Alzheimer's disease. Treatment with aducanumab-avwa should only be considered for initiation in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied. The efficacy of aducanumab-avwa was evaluated in two double-blind, randomized, placebo-controlled, parallel group studies. Of note, aducanumab received FDA approval based on a surrogate endpoint (reduction in amyloid-β plaques) and has not yet been shown to provide a clinical benefit. Aducanumab is a human immunoglobulin (IgG1) monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid-β, a defining pathophysiological feature of Alzheimer's disease.[12]

Lecanemab-irmb was approved in 2023 and is also indicated for the treatment of Alzheimer's disease. Treatment should only be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials. Lecanemab-irmb is a humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid beta. Accumulation of amyloid beta plaques in the brain is a defining pathophysiological feature of Alzheimer's disease. Lecanemab-irmb works by reducing amyloid beta plaques. Lecanemab-irmb was evaluated in two double-blind, placebo-controlled, parallel-group randomized studies.[13]

The Alzheimer's agents that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All products with the exception of memantine-donepezil, aducanumab-avwa, and lecanemab-irmb are available in a generic formulation. This class was last reviewed in May 2022.

Table 1. Alzheimer's Agents Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Parasympathomimetic (Cholinergic Agents)			
Donepezil	orally disintegrating tablet, tablet, transdermal patch	Adlarity®, Aricept®*	donepezil, Aricept®*
Galantamine	extended-release capsule, solution, tablet	N/A	galantamine
Rivastigmine	capsule, transdermal patch	Exelon®*	rivastigmine
Central Nervous System Agents, Miscellaneous			
Aducanumab-avwa	injection	Aduhelm®	none
Lecanemab-irmb	injection	Leqembi®	none
Memantine	extended-release capsule, solution, tablet	Namenda®*, Namenda XR®*	memantine
Combination Products			
Memantine and donepezil	extended-release capsule	Namzaric®	none

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the Alzheimer's agents are summarized in Table 2.

Table 2. Treatment Guidelines Using the Alzheimer's Agents

Clinical Guideline	Recommendation(s)
European Federation of Neurological Societies: **Guidelines for the Diagnosis and Management of Alzheimer's Disease (2010)[14]**	• Patients and caregivers should be provided with education and support. • There is insufficient evidence to support the use of any drugs purely for the primary prevention of dementia. Cholinesterase inhibitors, vitamin E, gingko and estrogens should not be used as treatments for those with mild cognitive impairment. • In patients with Alzheimer's disease, treatment with cholinesterase inhibitors (donepezil, galantamine, or rivastigmine) should be considered at the time of diagnosis, taking into account expected therapeutic benefits and potential safety issues. Benefits on cognitive and non-cognitive symptoms have been demonstrated in those with mild, moderate and severe disease. Realistic expectations for treatment effects and potential side effects should be discussed with the patient and caregivers. • In patients with moderate to severe Alzheimer's disease, treatment with memantine should be considered taking into account expected therapeutic benefits and potential safety issues. Benefits on cognitive and noncognitive symptoms are apparent, some non-cognitive symptoms (agitation, delusions) may respond better than others. Realistic expectations for treatment effects and potential side effects should be discussed with the patient and caregivers. • Regular patient follow-up should be an integral part of management. • Aspirin should not be used as a treatment for Alzheimer's disease, though it can be used in those with Alzheimer's disease who also have other indications for its use (e.g. to prevent cardiovascular events). • Vitamin E should not be used as a treatment for Alzheimer's disease. • Currently, there is insufficient evidence to support the use of other agents including, anti-inflammatory drugs, nootropics (including piracetam, nicergoline), selegiline, oestrogens, pentoxyphylins, or statins in the treatment or prevention of Alzheimer's disease. • Cognitive stimulation or rehabilitation may be considered in patients with mild to moderate Alzheimer's disease. • Management of behavioral and psychological symptoms of dementia should begin with a careful search for triggers and causative factors (i.e. physical

Clinical Guideline	Recommendation(s)
	illness). Where possible, initial treatment should be non-pharmacological. • Antipsychotics should only be used for moderate or severe behavioral and psychological symptoms of dementia causing significant distress which have either not responded to other treatments (like non-pharmacological measures or cholinesterase inhibitors) or when other treatments are not appropriate. Low dose of atypical agents should be used only after assessment of risk benefit and full discussion with patient (when capacity allows) and caregiver. • Atypical agents have fewer side effects and do not confer a greater risk of stroke or mortality than conventional drugs. • Selective serotonin reuptake inhibitors rather than tricyclic antidepressants should be used to treat depression in Alzheimer's disease.

National Institute for Health and Care Excellence: **Dementia: assessment, management and support for people living with dementia and their carers (2018)**[15]	<u>Pharmacological management of Alzheimer's disease</u>
	• The three acetylcholinesterase (AChE) inhibitors donepezil, galantamine and rivastigmine as monotherapies are recommended as options for managing mild to moderate Alzheimer's disease.
	• Memantine monotherapy is recommended as an option for managing Alzheimer's disease for people with:
	  o moderate Alzheimer's disease who are intolerant of or have a contraindication to AChE inhibitors or
	  o severe Alzheimer's disease.
	• For people with an established diagnosis of Alzheimer's disease who are already taking an AChE inhibitor:
	  o consider memantine in addition to an AChE inhibitor if they have moderate disease
	  o offer memantine in addition to an AChE inhibitor if they have severe disease.
	• Treatment should be under the following conditions:
	  o For people who are not taking an AChE inhibitor or memantine, prescribers should only start treatment with these on the advice of a clinician who has the necessary knowledge and skills. This could include:
	  ▪ secondary care medical specialists such as psychiatrists, geriatricians and neurologists
	  ▪ other healthcare professionals (such as general practitioners (GPs), nurse consultants and advanced nurse practitioners), if they have specialist expertise in diagnosing and treating Alzheimer's disease.
	  o Once a decision has been made to start an AChE inhibitor or memantine, the first prescription may be made in primary care.
	  o For people with an established diagnosis of Alzheimer's disease who are already taking an AChE inhibitor, primary care prescribers may start treatment with memantine without taking advice from a specialist clinician.
	  o Do not stop AChE inhibitors in people with Alzheimer's disease because of disease severity alone.
	• If prescribing an AChE inhibitor (donepezil, galantamine or rivastigmine), treatment should normally be started with the drug with the lowest acquisition cost (taking into account required daily dose and the price per dose once shared care has started). However, an alternative AChE inhibitor could be prescribed if it is considered appropriate when taking into account adverse event profile, expectations about adherence, medical comorbidity, possibility of drug interactions and dosing profiles.
	• When using assessment scales to determine the severity of Alzheimer's disease, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the results and make any adjustments they consider appropriate. Healthcare professionals should also be mindful of the need to secure equality of access to treatment for patients from different ethnic groups, in particular those from different cultural

Clinical Guideline	Recommendation(s)
	backgrounds. • When assessing the severity of Alzheimer's disease and the need for treatment, healthcare professionals should not rely solely on cognition scores in circumstances in which it would be inappropriate to do so. These include: o if the cognition score is not, or is not by itself, a clinically appropriate tool for assessing the severity of that patient's dementia because of the patient's learning difficulties or other disabilities (for example, sensory impairments), linguistic or other communication difficulties or level of education or o if it is not possible to apply the tool in a language in which the patient is sufficiently fluent for it to be appropriate for assessing the severity of dementia or o if there are other similar reasons why using a cognition score, or the score alone, would be inappropriate for assessing the severity of dementia. o In such cases healthcare professionals should determine the need for initiation or continuation of treatment by using another appropriate method of assessment. • Do not offer the following specifically to slow the progress of Alzheimer's disease, except as part of a randomized controlled trial: o diabetes medicines o hypertension medicines o statins o non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin. Pharmacological management of non-Alzheimer's dementia • Offer donepezil or rivastigmine to people with mild to moderate dementia with Lewy bodies. • Only consider galantamine for people with mild to moderate dementia with Lewy bodies if donepezil and rivastigmine are not tolerated. • Consider donepezil or rivastigmine for people with severe dementia with Lewy bodies. • Consider memantine for people with dementia with Lewy bodies if AChE inhibitors are not tolerated or are contraindicated. • Only consider AChE inhibitors or memantine for people with vascular dementia if they have suspected comorbid Alzheimer's disease, Parkinson's disease dementia or dementia with Lewy bodies. • Do not offer AChE inhibitors or memantine to people with frontotemporal dementia. • Do not offer AChE inhibitors or memantine to people with cognitive impairment caused by multiple sclerosis.
American Academy of Neurology: **Practice Guideline Update Summary: Mild Cognitive Impairment (2018)[16]** Reaffirmed January 30, 2021	<u>Pharmacologic treatments for patients diagnosed with mild cognitive impairment (MCI)</u> • Donepezil use over three years is possibly ineffective for reducing the chances of a progression to possible or probably Alzheimer dementia. In patients with MCI, it is unknown whether donepezil slows progression on various cognitive scales. • Galantamine use over 24 months is probably ineffective for reducing progression to dementia. • Rivastigmine use up to 48 months is possibly ineffective for reducing the rate of progression to possible or probable Alzheimer dementia. <u>Recommendations for management of MCI</u> • For patients diagnosed with MCI, clinicians should wean patients from medications that can contribute to cognitive impairment (where feasible and medically appropriate) and treat modifiable risk factors that may be contributing. • There are no FDA-approved medications for the treatment of MCI. Moreover, there are no high-quality, long-term studies identifying pharmacologic or dietary

Clinical Guideline	Recommendation(s)
	agents that either improve cognition or delay progression in patients with MCI. For patients diagnosed with MCI, clinicians should counsel the patients and families that there are no pharmacologic or dietary agents currently shown to have symptomatic cognitive benefit in MCI and that no medications are FDA-approved for this purpose. • Studies of cholinesterase inhibitors showed no benefit on cognitive outcomes or reduction in progression from MCI to dementia, although some studies could not exclude an important effect. In addition to lacking efficacy, side effects of cholinesterase inhibitors are common, including gastrointestinal symptoms and cardiac concerns. For patients diagnosed with MCI, clinicians may choose not to offer cholinesterase inhibitors. If clinicians choose to offer cholinesterase inhibitors, they must first discuss with patients the fact that this is an off-label prescription not currently backed by empirical evidence. • For patients diagnosed with MCI who are interested in pharmacologic treatment, clinicians may inform these patients of centers or organizations that can connect patients to clinical trials. • For patients diagnosed with MCI, clinicians should recommend regular exercise (twice per week) as part of an overall approach to management. • In patients with MCI, cognitive interventions may be beneficial in improving measures of cognitive function.
The Movement Disorder Society: **Evidence-Based Medicine Review Update: Treatments for the non-motor symptoms of Parkinson's disease (2019)**[17]	<u>Treatment of dementia in Parkinson's disease</u> • Rivastigmine is efficacious for the treatment of dementia in Parkinson's disease. • There is insufficient evidence for donepezil and galantamine for the treatment of dementia in Parkinson's disease. • Safety conclusions are that the acetylcholinesterase inhibitors donepezil, rivastigmine, and galantamine have an acceptable risk without specialized monitoring. • The practice implications are that rivastigmine is clinically useful for the treatment of dementia in Parkinson's disease, while the practice implications for donepezil and galantamine are that they are both possibly useful for the treatment of dementia in Parkinson's disease. • The practice implications for memantine are that it is investigational for the treatment of dementia in Parkinson's disease. <u>Treatment of non-dementia cognitive impairment in Parkinson's disease</u> • There is "insufficient evidence" to conclude on the efficacy of rivastigmine or rasagiline for the treatment of cognitive impairment in Parkinson's disease; practice implications are investigational.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the Alzheimer's agents are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Single Entity Alzheimer's Agents[4]

Indication	Parasympathomimetic (Cholinergic Agents)			Central Nervous System Agents, Miscellaneous		
	Donepezil	Galantamine	Rivastigmine	Aducanumab-avwa	Lecanemab-irmb	Memantine
Mild-to-moderate dementia of the Alzheimer's type		✔	✔ †			

Indication	Parasympathomimetic (Cholinergic Agents)			Central Nervous System Agents, Miscellaneous		
	Donepezil	Galantamine	Rivastigmine	Aducanumab-avwa	Lecanemab-irmb	Memantine
Mild, moderate, and severe dementia of the Alzheimer's type	✔		✔ ‡			
Moderate-to-severe dementia of the Alzheimer's type						✔
Mild-to-moderate dementia associated with Parkinson's disease			✔			
Treatment of Alzheimer's disease in patients with mild cognitive impairment or mild dementia stage of disease				✔	✔	

†Capsule and solution.
‡Transdermal patch.

Table 4. FDA-Approved Indications for the Combination Product Alzheimer's Agents[4]

Indication	Memantine and Donepezil
Moderate-to-severe dementia of the Alzheimer's type	✔ *

*In patients stabilized on 10 mg of donepezil hydrochloride once daily.

IV. Pharmacokinetics

The pharmacokinetic parameters of the Alzheimer's agents are listed in Table 5. Pharmacokinetic properties of the combination products are in line with the properties of their individual components listed below.

Table 5. Pharmacokinetic Parameters of the Alzheimer's Agents[5]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life
Parasympathomimetic (Cholinergic Agents)					
Donepezil	100	96	Liver (% not reported)	Renal (57) Feces (9 to 15)	70 hours*
Galantamine	90	18	Liver (75)	Renal (95) Feces (5)	7 hours
Rivastigmine	Oral: 36 to 72	40	Liver, extensive Brain, extensive	Renal (>90)	Oral: 1.4 to 1.7 hours Transdermal: 3.0 hours
Central Nervous System Agents, Miscellaneous					
Aducanumab-avwa	Not reported	Not reported	Liver (% not reported)	Not reported	24.8 days
Lecanemab-irmb	Not reported	Not reported	Degradation by proteolytic enzymes	Not reported	5 to 7 days
Memantine	Well absorbed	45	Liver, partial	Renal (48)	60 to 80 hours

* Half-life of 104 hours in subjects over 55 years of age.

V. Drug Interactions

Major drug interactions with the Alzheimer's agents are listed in Table 6.

Table 6. Major Drug Interactions with the Alzheimer's Agents[5]

Generic Name(s)	Interaction	Mechanism
Parasympathomimetic (Cholinergic Agents)		

Generic Name(s)	Interaction	Mechanism
Donepezil	Azole antifungals	Concomitant use of donepezil, a CYP3A4 substrate that is associated with prolongation of the QT interval, is contraindicated with certain drugs that prolong QT interval and strongly inhibit CYP3A4.
Donepezil	Anticholinergic agents	Concomitant use of a cholinesterase inhibitor, such as donepezil, and an anticholinergic agent may result in interference with the efficacy of both agents.
Donepezil	QT interval prolonging agents	Concurrent use of donepezil and QT interval prolonging agents may result in increased risk of QT-interval prolongation and torsade de pointes.
Donepezil	CYP3A4 inhibitors and inducers	Concurrent use of donepezil and CYP3A4 inhibitors/ inducers may result in increased/decreased donepezil exposure.
Donepezil	Select CYP2D6 inhibitors (clobazam, terbinafine, cinacalcet, peginterferon alfa-2b)	Concurrent use of donepezil and selected CYP2D6 inhibitors may result in increased donepezil exposure.
Donepezil	Seizure threshold lowering agents	Concurrent use of donepezil and seizure threshold lowering agents may result in reduced seizure threshold.
Galantamine	QT interval prolonging agents	Concurrent use of galantamine and QT interval prolonging agents may result in increased risk of QT-interval prolongation and torsade de pointes.
Rivastigmine	Metoclopramide	The concomitant use of metoclopramide and rivastigmine is contraindicated due to potential additive effects of extrapyramidal reactions.
Rivastigmine	Beta blockers	Concomitant use of rivastigmine and beta-blockers, especially cardioselective agents, is not recommended due to additive bradycardic effects resulting in syncope.
Central Nervous System Agents, Miscellaneous		
Memantine	Dextromethorphan, Amantadine, Ketamine	Concurrent use of memantine and selected N-methyl-D-aspartate antagonists may result in increased adverse events of N-methyl-D-aspartate antagonists.
Memantine	Carbonic anhydrase inhibitors	Concurrent use of memantine and carbonic anhydrase inhibitors may result in reduced clearance of memantine due to urinary alkalinization.

VI. Adverse Drug Events

The most common adverse drug events reported with the Alzheimer's agents are listed in Table 7. Adverse drug reactions associated with the combination products are in line with the individual components listed below.[4] Boxed warnings are listed in Table 8.

Table 7. Adverse Drug Events (%) Reported with the Single Entity Alzheimer's Agents[4,6-13]

Adverse Events	Parasympathomimetic (Cholinergic Agents)			Central Nervous System Agents, Miscellaneous		
	Donepezil	Galantamine	Rivastigmine	Aducanumab-avwa	Lecanemab-irmb	Memantine
Cardiovascular						
Angina pectoris	-	-	≥1	-	-	-
Atrial fibrillation	≥1	-	≥1	-	3	-
Bradycardia	≥1	2	≥1	-	-	-
Chest pain	1 to 2	≥1	-	-	-	-
Heart failure	-	-	≥1	-	-	≥1
Hemorrhage	2	-	-	-	<1	-
Hypertension	1 to 3	-	3	-	-	4
Hypotension	≥1	-	≥1	-	-	-

Adverse Events	Parasympathomimetic (Cholinergic Agents)			Central Nervous System Agents, Miscellaneous		
	Donepezil	Galantamine	Rivastigmine	Aducanumab-avwa	Lecanemab-irmb	Memantine
Myocardial infarction	-	-	≥1	-	-	-
Palpitation	-	-	≥1	-	-	-
Peripheral edema	≥1	-	-	-	-	≥2
Postural hypotension	-	-	≥1	-	-	-
Syncope	2	2	3	-	-	≥1
Vasodilation	≥1	-	-	-	-	-
Central Nervous System						
Abnormal crying	≥1	-	-	-	-	-
Abnormal dreams	3	-	-	-	-	-
Aggression	≥1	-	3	-	-	≥1
Agitation	-	-	≥1	-	-	≥2
Anxiety	-	-	4 to 5; 3*	-	-	≥2
Aphasia	≥1	-	-	-	-	-
Bradykinesia	-	-	≥1	-	-	-
Cerebrovascular accident	-	-	-	-	-	≥1
Confusion	2	-	1 to 8	8	-	6
Convulsion	≥1	-	≥1	-	-	-
Delusions	≥1	-	-	-	-	-
Depression	2 to 3	7	1 to 6; 4*	-	-	≥2
Dizziness	2 to 8	9	6 to 21; 2 to 7*	-	-	7
Dyskinesia	-	-	≥1	-	-	-
Emotional lability	2	-	-	-	-	-
Fatigue	5	5	4 to 9; 2*	-	-	2
Gait abnormality	-	-	≥1	-	-	≥2
Hallucination	3	-	4	-	-	3
Headache	3 to 10	8	4 to 17; 3 to 4*	21	11 to 14	6
Hostility	3	-	-	-	-	-
Hypokinesia	-	-	-	-	-	≥1
Insomnia	2 to 14	5	3 to 9; 1 to 4*	-	-	≥2
Irritability	≥1	-	-	-	-	-
Malaise	-	≥1	5	-	-	-
Nervousness	1 to 3	-	-	-	-	-
Paranoid reaction	-	-	≥1	-	-	-
Paresthesia	≥1	-	≥1	-	-	-
Parkinson's disease worsening	-	-	3	-	-	-
Parkinsonism	-	-	2	-	-	-
Personality disorder	2	-	-	-	-	-
Restlessness	≥1	-	≥1	-	-	-
Somnolence	2	4	4 to 5	-	-	3
Transient ischemic attack	-	-	≥1	-	-	≥1
Tremor	≥1	3	4 to 10; ≥1*	-	-	-
Vertigo	≥1	-	≥1; 0 to 2*	-	-	≥1
Wandering	≥1	-	-	-	-	-
Dermatological						
Diaphoresis	≥1	-	4	-	-	-
Eczema	3	-	-	-	-	-
Pruritus	≥1	-	≥1*	-	-	-
Rash	≥1	-	≥1	-	6	≥1
Skin ulcer	≥1	-	-	-	-	-
Urticaria	≥1	-	-	-	-	-

Adverse Events	Parasympathomimetic (Cholinergic Agents)			Central Nervous System Agents, Miscellaneous		
	Donepezil	Galantamine	Rivastigmine	Aducanumab-avwa	Lecanemab-irmb	Memantine
Gastrointestinal						
Abdominal pain	≥1	5	4 to 13; 2 to 4*	-	-	-
Anorexia	4 to 8	7 to 9	6 to 17; 3 to 9*	-	-	≥2
Bloating	≥1	-	-	-	-	-
Constipation	≥1	-	5; ≥1*	-	-	5
Diarrhea	5 to 15	6 to 12	7 to 19; 6 to 10*	9	8	≥2
Dyspepsia	≥1	5	1 to 9	-	-	-
Epigastric pain	≥1	-	-	-	-	-
Eructation	-	-	2	-	-	-
Fecal incontinence	≥1	-	≥1	-	-	-
Flatulence	-	≥1	4	-	-	-
Gastritis	-	-	≥1; ≥1*	-	-	-
Gastrointestinal bleeding	≥1	-	-	-	-	-
Nausea	3 to 19	13 to 24	29 to 47; 7 to 21*	-	6	≥2
Toothache	≥1	-	-	-	-	-
Vomiting	3 to 9	6 to 13	17 to 31; 6 to 19*	-	6	3
Weight decrease	1 to 3	5 to 7	3; 3 to 8*	-	-	≥1
Genitourinary						
Cystitis	≥1	-	-	-	-	-
Frequent urination	2	-	-	-	-	≥1
Glycosuria	≥1	-	-	-	-	-
Hematuria	≥1	3	≥1	-	-	-
Libido increased	≥1	-	-	-	-	-
Urinary incontinence	2	≥1	≥1*	-	-	≥2
Urinary tract infection	≥1	8	7; 2*	-	-	≥2
Laboratory Test Abnormalities						
Alkaline phosphatase increased	≥1	-	-	-	-	≥1
Creatinine increased	3	-	-	-	-	-
Hyperlipemia	2	-	-	-	-	-
Hypokalemia	-	-	≥1	-	-	-
Lactate dehydrogenase increased	≥1	-	-	-	-	-
Musculoskeletal						
Arthralgia	-	-	-	-	-	≥2
Arthritis	1 to 2	-	≥1	-	-	-
Asthenia	≥1	≥1	2 to 6; 2 to 3*	-	-	-
Ataxia	≥1	-	≥1	-	-	≥1
Back pain	3	-	≥1	-	-	3
Bone fracture	≥1	-	-	-	-	-
Leg cramps	-	-	≥1	-	-	-
Muscle cramps	3 to 8	-	-	-	-	-
Myalgia	-	-	≥1	-	-	-
Rigors	-	-	≥1	-	-	-
Respiratory						
Bronchitis	≥1	-	-	-	-	≥2
Cough increased	≥1	-	-	-	9	4
Dyspnea	≥1	-	≥1	-	-	2
Pharyngitis	≥1	-	-	-	-	-
Pneumonia	≥1	-	≥1*	-	-	≥1

Adverse Events	Parasympathomimetic (Cholinergic Agents)			Central Nervous System Agents, Miscellaneous		
	Donepezil	Galantamine	Rivastigmine	Aducanumab-avwa	Lecanemab-irmb	Memantine
Respiratory tract infection	-	-	-	-	-	≥2
Rhinitis	-	4	4	-	-	-
Sore Throat	≥1	-	-	-	-	-
Special Senses						
Blurred vision	≥1	-	-	-	-	-
Cataract	≥1	-	≥1	-	-	≥1
Conjunctivitis	-	-	-	-	-	≥1
Eye irritation	≥1	-	-	-	-	-
Tinnitus	-	-	≥1	-	-	-
Other						
Accident	7 to 13	-	-	-	-	-
Accidental trauma	-	-	1 to 10	-	-	-
Allergy	-	-	≥1	-	-	-
Anemia	-	3	≥1; ≥1*	-	-	≥1
ARIA-E	-	-	-	35	10 to 13	-
ARIA-H microhemorrhage	-	-	-	19	6 to 17	-
ARIA-H superficial siderosis	-	-	-	15	6 to 17	-
Dehydration	1 to 2	-	1 to 2; ≥1*	-	-	-
Ecchymosis	4 to 5	-	-	-	-	-
Edema	≥1	-	≥1	-	-	-
Epistaxis	-	-	≥1	-	-	-
Fall	-	-	≥1*	15	-	≥2
Fever	2	≥1	≥1	-	-	-
Flu syndrome	≥1	-	3	-	-	≥2
Hot flashes	≥1	-	≥1	-	-	-
Infection	1 to 11	-	-	-	-	-
Inflicted injury	-	-	-	-	-	≥2
Influenza	≥1	-	-	-	-	-
Infusion-related reaction	-	-	-	-	20 to 26	-
Lymphocytopenia	-	-	-	-	4	-
Pain	3 to 9	-	-	-	-	3

ARIA-E=amyloid-related imaging abnormalities-edema, ARIA-H=Amyloid-related imaging abnormalities-hemosiderin deposition
✔ Percent not specified.
- Event not reported or incidence <1%.
*Transdermal patch.

Table 8. Boxed Warning for aducanumab-avwa and lecanemab-irmb[12,13]

WARNING: AMYLOID RELATED IMAGING ABNORMALITIES

Monoclonal antibodies directed against aggregated forms of beta amyloid, including ADUHELM/LEQEMBI, can cause amyloid related imaging abnormalities (ARIA), characterized as ARIA with edema (ARIA-E) and ARIA with hemosiderin deposition (ARIA-H).

Incidence and timing of ARIA vary among treatments. ARIA usually occurs early in treatment and is usually asymptomatic, although serious and life-threatening events rarely can occur. Serious intracerebral hemorrhages, some of which have been fatal, have been observed in patients treated with this class of medications.

ApoE ε4 Homozygotes

Patients who are apolipoprotein E ε4 (ApoE ε4) homozygotes (approximately 15% of Alzheimer's disease patients) treated with this class of medications, including ADUHELM/LEQEMBI, have a higher incidence of ARIA, including symptomatic, serious, and severe radiographic ARIA, compared to heterozygotes and noncarriers. Testing for ApoE ε4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA. Prior to testing, prescribers should discuss with patients the risk of ARIA across genotypes and the implications of genetic testing results. Prescribers should inform patients that if genotype testing is not performed they can still be treated with ADUHELM/LEQEMBI; however, it cannot be determined if they are ApoE ε4 homozygotes and at higher risk for ARIA.

Consider the benefit of ADUHELM/LEQEMBI for the treatment of Alzheimer's disease and potential risk of serious adverse events associated with ARIA when deciding to initiate treatment with ADUHELM/LEQEMBI.

VII. Dosing and Administration

The usual dosing regimens for the Alzheimer's agents are listed in Table 9.

Table 9. Usual Dosing Regimens for the Alzheimer's Agents[4,6-12]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Parasympathomimetic (Cholinergic Agents)			
Donepezil	Dementia of the Alzheimer's type (mild, moderate, severe): Tablet and orally disintegrating tablet: initial, 5 mg daily; may increase to 10 mg daily after four to six weeks; maintenance, 5 to 10 mg daily Transdermal patch: initial, 5 mg per 24-hour patch applied weekly, may increase to 10 mg per patch applied once weekly after four to six weeks (maximum 10 mg per 24 hours)	Safety and efficacy not established in the pediatric population.	Orally disintegrating tablet: 5 mg 10 mg Tablet: 5 mg 10 mg 23 mg Transdermal patch: 5 mg/24 hours 10 mg/24 hours
Galantamine	Mild-to-moderate dementia of the Alzheimer's type: Extended-release capsule: initial, 8 mg daily; maintenance, 16 to 24 mg daily Oral solution, tablet: initial, 4 mg twice a day with the morning and evening meals; maintenance: 8 to 12 mg twice a daily	Safety and efficacy not established in the pediatric population.	Extended-release capsule: 8 mg 16 mg 24 mg Tablet: 4 mg 8 mg 12 mg Solution: 4 mg/mL
Rivastigmine	Mild-to-moderate dementia of the Alzheimer's type: Capsule: initial, 1.5 mg twice daily with the morning and evening meals; maintenance, 3 to 6 mg twice daily Transdermal patch: initial, 4.6 mg/24 hours; maintenance, 9.5 or 13.3 mg/24 hours Severe dementia of the Alzheimer's type: Transdermal patch: initial, 4.6 mg/24 hours; maintenance, 13.3 mg/24 hours Mild-to-moderate dementia associated with Parkinson's disease: Capsule: initial, 1.5 mg twice daily	Safety and efficacy not established in the pediatric population.	Capsule: 1.5 mg 3 mg 4.5 mg 6 mg Transdermal patch: 4.6 mg/24 hours 9.5 mg/24 hours 13.3 mg/24 hours

<table>
<tr><th>Generic Name(s)</th><th>Usual Adult Dose</th><th>Usual Pediatric Dose</th><th>Availability</th></tr>
<tr><td></td><td>with the morning and evening meals; maintenance, 3 to 6 mg twice daily

Transdermal patch: initial, 4.6 mg/24 hours; maintenance, 9.5 or 13.3 mg/24 hours</td><td></td><td></td></tr>
<tr><td colspan="4">Central Nervous System Agents, Miscellaneous</td></tr>
<tr><td>Aducanumab-avwa</td><td>Alzheimer's disease in patients with mild cognitive impairment or mild dementia stage of disease:
Solution for IV injection: infuse every four weeks based on the following titration:
<table><tr><th>Infusion (every four weeks</th><th>Dose</th></tr><tr><td>1 and 2</td><td>1 mg/kg</td></tr><tr><td>3 and 4</td><td>3 mg/kg</td></tr><tr><td>5 and 6</td><td>6 mg/kg</td></tr><tr><td>7 and beyond</td><td>10 mg/kg</td></tr></table></td><td>Safety and efficacy not established in the pediatric population.</td><td>Injection:
170 mg/1.7 mL
300 mg/3 mL</td></tr>
<tr><td>Lecanemab-irmb</td><td>Alzheimer's disease in patients with mild cognitive impairment or mild dementia stage of disease:
Solution for IV injection: : 10 mg/kg as an IV infusion once every two weeks</td><td>Safety and efficacy not established in the pediatric population.</td><td>Injection:
200 mg/2 mL
500 mg/5 mL</td></tr>
<tr><td>Memantine</td><td>Moderate-to-severe dementia of the Alzheimer's type:
Solution and tablet: initial, 5 mg once daily, increase dose by 5 mg at weekly intervals (twice daily dosing); maintenance, 10 mg twice daily

Extended release capsule: initial, 7 mg once daily; maintenance, 28 mg once daily</td><td>Safety and efficacy not established in the pediatric population.</td><td>Extended release capsule:
7 mg
14 mg
21 mg
28 mg

Extended release capsule dose pack:
7 mg (7 count)-14 mg (7 count)-21 mg (7 count)-28 mg (7 count)

Solution:
10 mg/5 mL

Tablet:
5 mg
10 mg

Tablet dose pack:
5 mg (28 count)-10 mg (21 count)</td></tr>
<tr><td colspan="4">Combination products</td></tr>
<tr><td>Memantine and donepezil</td><td>Moderate-to-severe dementia of the Alzheimer's type:
Extended release capsule: patients stabilized on memantine hydrochloride (10 mg twice daily or 28 mg extended-release once daily) and donepezil hydrochloride 10 mg can be switched to 28 mg-10 mg combination capsule,</td><td>Safety and efficacy not established in the pediatric population.</td><td>Extended release capsule:
7-10 mg
14-10 mg
21-10 mg
28-10 mg

Extended release</td></tr>
</table>

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	taken once a day in the evening		capsule dose pack: 7-10 mg (7 count)-14-10 mg (7 count)-21-10 mg (7 count)-28-10 mg (7 count)

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the Alzheimer's agents are summarized in Table 10.

Table 10. Comparative Clinical Trials with the Alzheimer's Agents

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dementia of Alzheimer's Disease				
Geldmacher et al.[18] (2003) Donepezil 5 mg/day	OS Patients with Alzheimer's disease	N=1,115 Variable duration	Primary: Time to nursing home placement Secondary: Not reported	Primary: Use of donepezil of 5 mg/day or more was associated with significant delays in nursing home placement. A cumulative dose-response relationship was observed between longer-term sustained donepezil use and delay of nursing home placement. When donepezil was taken at effective doses for at least nine to 12 months, conservative estimates of the time gained before nursing home placement were 21.4 months for first-dementia-related nursing home placement and 17.5 months for permanent nursing home placement. Secondary: Not reported
Burns et al.[19] (2007) Donepezil 5 to 10 mg/day	MC, OL Patients ≥50 years of age with mild-to-moderate Alzheimer's disease	N=579 132 weeks	Primary: ADAS-cog, CDR-SB, IDDD, QoLS, and adverse events Secondary: Not reported	Primary: Mean changes in ADAS-cog scores of all patients were improved by approximately two points after six weeks (cumulative week 36) and one point after 12 weeks (cumulative week 42), with improvement compared to the start of OL treatment. At week 24 (cumulative week 54), mean ADAS-cog scores still showed improvement (approximately 0.5 points) compared to those scores reported at the start of OL treatment. From 24 weeks, ADAS-cog scores declined over the remainder of the study. At the end of 132 weeks of OL treatment (162 weeks total follow-up), the change from DB baseline was 15.6 points for all patients. No difference was seen between patients who had previously received placebo in the DB phase vs those receiving donepezil for the entire treatment period. CDR-SB scores improved slightly over the first 12 weeks (up to cumulative week 42) of OL treatment and then slowly declined for the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				remainder of the study period (up to cumulative week 162). Mean IDDD total scores were maintained over the first 24 weeks of OL treatment to within approximately 1 point relative to those at the beginning of this study period. Mean IDDD scores were 138.1 at week 0, 136.9 at week 12, 138.9 at week 24 and 170.8 at week 132 (162 weeks of total follow-up). At the start of the OL extension, QoLS scores were improved compared to baseline, with a mean change of 3.03. The scores remained above the baseline level at weeks six and 12 of OL treatment. At the end of 132 weeks of OL treatment, the decline from the baseline for the DB study was -46.2. Overall, 85% of patients experienced at least one treatment-emergent adverse event. The most common adverse events included diarrhea (12%), nausea (11%), infection (11%) and accidental injury (10%). Nonfatal all-causality and treatment-related serious adverse events were reported for 25 and 7% of patients, respectively. Seventeen patients died during the study or within four weeks after discontinuation of donepezil. The most common causes of death were pneumonia (seven patients) and cerebrovascular accident (two patients). Fifteen deaths were considered unrelated to donepezil. Two deaths, one due to a cerebral hemorrhage diagnosed on day five of treatment and another due to a suspected myocardial infarction on day 55, were considered by the investigators to be possibly related to donepezil. Secondary: Not reported
Hashimoto et al.[20] (2009) Donepezil 5 mg/day	OS, PRO Patients with Alzheimer's disease	N=416 12 weeks	Primary: MMSE Secondary: Not reported	Primary: There were significant changes in mean scores on the MMSE (0.9; P<0.01) from baseline to week 12. There was a significant decrease in the personal strain score at week 12 (P=0.002). There was no significant improvement was in role strain.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was no significant decrease in the time spent supervising Alzheimer's disease patients. Secondary: Not reported
Homma et al.[21] (2009) Donepezil 10 mg/day	OL Japanese patients ≥50 years of age with severe Alzheimer's disease (modified Hachinski Ischemic Score ≤6, FAST ≥6, MMSE score of 1 to 12	N=189 52 weeks	Primary: SIB, and BEHAVE-AD Secondary: Not reported	Primary: The mean change in SIB scores during the OL study showed improvement until week 24, followed by a decline by week 36. For those patients receiving 52 weeks of treatment, the mean change in SIB from baseline (enrollment in OL study) was –6.1. The mean change in SIB declined more rapidly after 24 weeks. For the BEHAVE-AD, little change was observed during the OL study. The change from baseline to week 24 and week 52 was 0.7 and 0.5, respectively. The level of behavioral symptoms in the study population was low. Overall, 177 patients (93.7%) experienced at least one adverse event. Severe adverse events were reported by 15 patients (7.9%) and serious adverse events were reported by 33 patients (17.5%). The most common adverse events were nasopharyngitis, diarrhea, nausea and vomiting. Secondary: Not reported
Courtney et al.[22] (2004) Donepezil 5 to 10 mg/day vs placebo	DB, RCT Patients with Alzheimer's disease	N=565 156 weeks	Primary: MMSE, BADLS, time to entering institution Secondary: Not reported	Primary: Cognition averaged 0.8 MMSE points better (95% CI, 0.5 to 1.2; P<0.0001) and functionality 1.0 BADLS points better (95% CI, 0.5 to 1.6; P<0.0001) with donepezil over the first two years. No significant benefits were seen with donepezil compared to placebo in institutionalization (42 vs 44% at three years; P=0.4) or progression of disability (58 vs 59% at three years; P=0.4). The RR of entering institutional care in the donepezil group compared to placebo was 0.97 (95% CI, 0.72 to 1.30; P=0.8); the RR of progression of disability or entering institutional care was 0.96 (95% CI, 0.74 to 1.24; P=0.7).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Similarly, no significant differences were seen between donepezil and placebo in behavioral and psychological symptoms, caregiver psychopathology, adverse events or deaths, or between 5 and 10 mg donepezil. Secondary: Not reported
Sabbagh et al.[23] (2013) Donepezil 23 or 10 mg/day	Post hoc of a 24-week, DB, RCT Patients with moderate to severe Alzheimer's disease (baseline MMSE 0 to 20)	N= Duration not specified	Primary: Cognitive changes in subgroups of patients based on selected baseline and demographic characteristics Secondary: Not reported	Primary: Donepezil 23 mg/day provided statistically significant incremental cognitive benefits over donepezil 10 mg/day irrespective of baseline functional severity, measured by scores on the ADCS-ADL -severe version (P<0.05). When patients were categorized by baseline cognitive severity (MMSE score), significant benefits of donepezil 23 mg/day over 10 mg/day were seen in both subgroups when based on MMSE scores of 0 to 9 vs 10 to 20 (P<0.02 and P<0.01, respectively), and in the more severe subgroup when based on MMSE scores of 0 to 16 vs 17 to 20 (P<0.0001 and P>0.05). Statistically significant incremental cognitive benefits of donepezil 23 mg/day over 10 mg/day were also observed regardless of age, gender, weight, or pre-study donepezil 10mg/day treatment duration (P<0.05). In the multivariate analysis, the only significant interaction was between treatment and baseline MMSE score. Secondary: Not reported
Tariot et al.[24] (2012) Donepezil 23 mg/day	OL Patients with Alzheimer's disease	N=915 12 months	Primary: Safety analyses comprised examination of the incidence, severity, and timing of treatment-emergent adverse events;	Primary: In total, 674 patients (74.7%) reported at least one adverse event; in 320 of these patients (47.5%) at least one adverse event was considered to be possibly or probably study drug related. The majority of patients reporting adverse events (81.9%) had adverse events of mild or moderate severity. There were 268 patients (29.7%) who discontinued early, of which 123 (13.6%) were due to adverse events.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			changes in weight, electrocardiogram, vital signs, and laboratory parameters; and discontinuation due to adverse events all at months three, six, nine, and 12 Secondary: Not reported	Patients who had increased donepezil dose from 10 mg/day to 23 mg/day had slightly higher rates of adverse events than patients who were already receiving 23 mg (78.0 and 16.9 vs 72.8 and 14.0%, respectively). The incidence of new adverse events declined rapidly after the first two weeks and remained low throughout the duration of the study. Secondary: Not reported
Winblad et al.[25] (2006) RCT Donepezil 10 mg/day vs placebo OL Donepezil 5 mg daily for 28 days, then 10 mg/day per clinician's judgment	DB, OL, PC Patients 40 to 90 years of age with a probable or possible diagnosis of Alzheimer's disease	N=286 52-week RCT with a 2-year OL extension phase	Primary: GBS Secondary: MMSE, GDS, PDS, NPI	Primary: The GBS total scores indicate that both the continuous-treatment group and delayed-start groups had declined, with the difference between the two groups favoring the continuous-donepezil group, over the three-year period (P=0.056). Secondary: The MMSE declined significantly less in the continuous-treatment group than in the delayed-start group over the course of the study (P=0.004, P=0.057, respectively). GDS declined significantly less over the three-year study period in patients in the continuous-treatment group than in those in the delayed-start group (P=0.0231). There was a trend favoring continuous-donepezil treatment over delayed-start treatment on the PDS, although it was not statistically significant (P=0.091). NPI results showed no significant treatment differences between the groups.
Rogers et al.[26] (1998) Donepezil 5	DB, MC, PC, RCT Patients with mild-to-moderate	N=473 24 weeks	Primary: ADAS-Cog, CIBIC Secondary:	Primary: Out of 473 patients, 80% of placebo patients, 85% of 5 mg patients and 68% of 10 mg patients completed the study. Those that discontinued due to adverse effects were 7, 6, and 16% in the placebo, 5 and 10 mg groups,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day vs donepezil 10 mg/day vs placebo	Alzheimer's disease		Not reported	respectively. Primary outcome measure was mean change in scores from baseline to endpoint in the ADAS-Cog. Both donepezil doses were statistically better than placebo (P<0.0001). Global functioning as measured by the CIBIC plus were statistically better for both donepezil groups compared to placebo at endpoint (P<0.005). Donepezil 5 and 10 mg treatment showed no statistical difference in improvements. Secondary: Not reported
Winblad et al.[27] (2006) Donepezil 10 mg/day vs placebo	DB, PC, PG Patients ≥50 years of age with severe Alzheimer's disease (MMSE score of 1 to 10 and a FAST rating of stage 5 to 7c)	N=248 6 months	Primary: SIB Secondary: MMSE, NPI, and CGI-I	Primary: At six months, patients assigned donepezil had significantly better mean change from baseline scores than those taking placebo for SIB (P<0.05). Secondary: CGI-I scores and the mean change from screening scores on the MMSE at six- month follow-up favored donepezil treatment over placebo (all P<0.05). There was no significant difference between treatment groups on the NPI for the modified intention-to-treat population (P=0.43).
Black et al.[28] (2007) Donepezil 10 mg/day vs placebo	DB, MC, PC, RCT Patients ≥50 years of age with severe Alzheimer's disease (MMSE score of 1 to 12, modified Hachinski Ischemic score ≤6, and FAST score ≥6)	N=343 24 weeks	Primary: SIB and CIBIC-Plus Secondary: ADCS-ADL-sev, NPI, MMSE, CBQ, RUSP	Primary: Donepezil was more efficacious when compared to placebo on SIB score change from baseline to endpoint, as well as on CIBIC-Plus score (P<0.05 for all results). Secondary: On the ADCS-ADL-sev, both the donepezil group and the placebo group declined from baseline, and the treatment difference was NS (P=0.3574). On the NPI, donepezil was not significantly different from placebo (P=0.4612).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The donepezil group showed significant improvement from screening to endpoint on the MMSE compared to placebo (P=0.0267). The CBQ stress measure showed no significant change from baseline for either group. The RUSP scores also had low average responses with little movement from baseline and no significant differences.
Homma et al.[29] (2008) Donepezil 5 to 10 mg/day vs placebo	DB, MC, PC, RCT Japanese patients ≥50 years of age with severe Alzheimer's disease (modified Hachinski Ischemic Score ≤6, FAST ≥6, MMSE score of 1 to 12 and diagnosis confirmed by neuroimaging)	N=302 24 weeks	Primary: SIB and CIBIC-Plus Secondary: ADCS-ADL-sev and BEHAVE-AD	Primary: Donepezil 5 and 10 mg/day were more effective than placebo on the SIB. At week 24, patients in the donepezil 5 mg/day group had a significant change from baseline of 2.5 points and those in the donepezil 10 mg/day group had a significant change from baseline of 4.7 points. Patients in the placebo group showed significant worsening (–4.2 points) during the course of the study (P<0.001 vs placebo). For the CIBIC-Plus, the analysis was performed on the seven categories of change as well as the three collapsed categories of improved, no change and worsened. In the seven-category analysis, the distribution of CIBIC-Plus scores in the donepezil 10 mg/day group was better than placebo (P=0.003); however, there was no difference with 5 mg/day (P=0.151). In the collapsed-category analysis, the distribution of CIBIC-Plus scores in the donepezil 10 mg/day group was better than placebo (P=0.001); however, there was no difference with 5 mg/day (P=0.129). Secondary: For the ADCS-ADL-sev, there was no significant differences between donepezil and placebo (placebo group, –1.1 points; donepezil 5 mg/day group, –0.1 points; donepezil 10 mg/day group, –0.3 points). For the BEHAVE-AD, there was no significant differences between donepezil and placebo (placebo group, –0.5; donepezil 5 mg/day group, –0.5; donepezil 10 mg/ day group, –0.1). Treatment-emergent adverse events were reported by 73.3% of placebo patients, 78.2% of donepezil 5 mg/day patients and 83.3% of donepezil 10 mg/day patients. There was no significant difference in adverse events

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				between the donepezil groups and the placebo group. The most common adverse events reported are consistent with the known cholinergic side effects of donepezil. Serious adverse events were reported by 15 placebo patients (14.3%), 12 donepezil 5 mg/day patients (11.9%) and 10 donepezil 10 mg/day patients (10.4%). Five patients died during the treatment period. The causes of death were acute pneumonia (placebo group), acute myocardial infarction (donepezil 5 mg/day group), suspected stomach cancer (donepezil 5 mg/day group; the patient died 80 days after discontinuation), vomit-induced tracheal occlusion (donepezil 10 mg/day group; the patient died seven days after completion) and arrhythmia (donepezil 10 mg/day group).
Birks et al.[30] (2006) Donepezil 5 to 10 mg/day vs placebo	MA Patients with Alzheimer's disease	N=5,796 (24 trials) 12 to 60 weeks	Primary: ADAS-Cog, MMSE, CIBIC-Plus, ADL, withdrawals and adverse events Secondary: Not reported	Primary: A significant difference was seen on the ADAS-Cog scale for patients treated with donepezil 5 mg at 24 weeks (WMD, -2.02 points; 95% CI, -2.77 to -1.26; P<0.00001) and 10 mg at 24 weeks (WMD,–2.81 points; 95% CI, –3.55 to –2.06; P<0.00001). A significant difference was seen on the MMSE for patients treated with donepezil 10 mg/day as compared to placebo at 52 weeks (WMD, 1.84 points; 95% CI, 0.53 to 3.15; P=0.006). Global Clinical State, CIBIC-Plus scores showed significant benefit in patients treated with donepezil 5 and 10 mg/day (OR, 2.38; 95% CI, 1.78 to 3.19; P<0.00001 and OR, 1.82; 95% CI, 1.42 to 2.35; P<0.00001). Improvements were seen in ADL scores for patients in the donepezil group over those in the placebo group (P<0.01 for all scales used). Significantly more patients treated with donepezil 10 mg/day withdrew from treatment (24 vs 20%; P=0.003); however, there was no difference in withdrawal rates between the 5 mg/day and placebo group (P=0.56). Adverse events that occurred significantly more frequently in both the 5 and 10 mg/day treatment groups as compared to placebo are: anorexia, diarrhea, and muscle cramps. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Wallin et al.[31] (2007) Donepezil 5 to 10 mg/day vs historical data	MC, PRO Patients ≥40 years of age with probable Alzheimer's disease	N=435 3 years	Primary: MMSE, ADAS-Cog, CIBIC, IADL Secondary: Not reported	Primary: For the MMSE, patients had a mean score of 22.0 at baseline and 19.1 at 36 months. After 36 months of donepezil treatment, the mean decline was 3.8 points (95% CI, 3.0 to 4.7). For ADAS-Cog, patients had a mean score of 20.7 at baseline and 26.1 at 36 months. After 36 months, the mean increase was 8.2 points (95% CI, 6.4 to 10.0). A modeling equation predicts an increase in ADAS-Cog to be 4 to 9 points in 12 months without treatment. Scores for the treatment group were significantly better than predicted scores for non-treatment (95% CI, 14.5 to 16.6). For CIBIC, at two months, 34% of patients were considered improved, 59% unchanged and 7% were worse. At six months, 28% of patients were considered improved, 46% unchanged and 26% were worse. At 12 months, 20% of patients were considered improved, 29% unchanged and 51% were worse. At 36 months, 30% of patients were considered improved or unchanged. The IADL change from baseline at six months was 1.01, at 12 months 2.19, and at 36 months 6.18. Secondary: Not reported
Farlow et al.[32] (2010) Donepezil 10 mg/day vs donepezil 23 mg/day	DB, MC, RCT Patients 45 to 90 years of age with moderate-to-severe Alzheimer's disease who took donepezil 10 mg/day ≥12 weeks	N=1,467 24 weeks	Primary: Efficacy as measured by SIB-cognition and CIBIC-global function rating; tolerability Secondary: Not reported	Primary: After 24 weeks, the change in SIB-cognition score was significantly greater with donepezil 23 mg/day compared to donepezil 10 mg/day (2.6 vs 0.4, respectively; P<0.001). There was no significant different in CIBIC score with donepezil 23 mg/day compared to donepezil 10 mg/day (4.23 vs 4.29, respectively). In a post-hoc analysis, the least square mean changes in SIB score and CIBIC treatment effect at end point were greater with donepezil 23 mg/day compared to donepezil 10 mg/day in patients with more advanced Alzheimer's disease compared to less impaired patients (SIB, 1.6 vs -1.5,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				respectively; P<0.001; CIBIC, 4.31 vs 4.42; P=0.028). Treatment emergent adverse events were reported in 73.7% of patients who received donepezil 23 mg/day and in 63.7% of patients who received donepezil 10 mg/day. Adverse events were reported as follows with donepezil 23 mg/day: mild (30.8%), moderate (34.5%), and severe (8.4%). The most common treatment emergent adverse events were nausea (6.1%), vomiting (5%) and diarrhea (3.2%). Severe treatment emergent adverse events that were reported included nausea (0.9%), dizziness (0.7%) and vomiting (0.6%). Adverse events were reported as follows with donepezil 10 mg/day: mild (31.2%), moderate (25.3%), and severe (7.2%). The most common treatment emergent adverse events were nausea (1.9%), vomiting (0.8%) and diarrhea (1.5%). Severe treatment emergent adverse events that were reported included nausea (0.2%) and dizziness (0.2%). Secondary: Not reported
Ferris et al.[33] (2011) Donepezil 10 mg/day vs donepezil 23 mg/day	DB, MC, RCT (post-hoc analysis) Patients 45 to 90 years of age with moderate-to-severe Alzheimer's disease who took donepezil 10 mg/day ≥12 weeks	N=1,467 24 weeks	Primary: SIB-Language scale and 21-item SIB-derived language scale Secondary: Correlation of SIB-Language scale and SIB-derived language scale with ADCS-ADL-sev, CIBIC-plus/CIBIC-plus, and MMSE	Primary: At week 24, there was an improvement in language noted with donepezil 23 mg/day compared to a decline in language function with donepezil 10 mg/day (SIB-Language scale treatment difference, 0.8; P=0.0013, SIB-derived language scale treatment difference, 0.8; P=0.0009). Secondary: At week 24, SIB-Language scale and SIB-derived language scale scores were moderately correlated with scores on the ADCS-ADL-sev and CIBIC-plus. Results were similar in both moderate (MMSE, 17 to 20) and severe (MMSE, 0 to 16) Alzheimer's disease patients.
Farlow et al.[34] (2011)	DB, MC, RCT (post-hoc analysis)	N=1,434	Primary: Safety and	Primary: Of the 963 patients receiving donepezil 23 mg/day and 471 patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Donepezil 10 mg/day vs donepezil 23 mg/day	Patients 45 to 90 years of age with moderate-to-severe Alzheimer's disease who took donepezil 10 mg/day ≥12 weeks	24 weeks	tolerability Secondary: Not reported	receiving donepezil 10 mg/day, a total of 71.1 and 84.7% completed the study, respectively. The most common adverse events causing early discontinuation were higher in the donepezil 23 mg/day group compared to the donepezil 10 mg/day group (18.6 vs 7.9%, respectively). Adverse events that contributed the most to the discontinuations were vomiting (2.9 vs 0.4%, respectively), nausea (1.9 vs 0.4%, respectively), diarrhea (1.7 vs 0.4%, respectively), and dizziness (1.1 and 0%, respectively). The most common adverse events with donepezil 23 mg/day compared to donepezil 10 mg/day were nausea (11.8 vs 3.4%, respectively), vomiting (9.2 vs 2.5%, respectively) and diarrhea (8.3 vs 5.3%, respectively). Serious adverse events occurred in 8.3% of patients receiving donepezil 23 mg/day and in 9.6% of patients receiving donepezil 10 mg/day. These included urinary tract infection (0.6 vs 0.4%, respectively), fall (0.6 vs 0.4%, respectively), pneumonia (0.3 vs 0.6%, respectively), syncope (0.2 vs 1.1%, respectively), aggression (0.2 vs 0.8%, respectively), and confusional state (0.1 vs 0.6%, respectively). Secondary: Not reported
Doody et al.[35] (2012) Donepezil 23 mg/day vs donepezil 10 mg/day Patients were allowed to also take memantine.	DB, MC Patients with moderate-to-severe Alzheimer's disease	N=not specified 24 weeks	Primary: Efficacy and safety Secondary: Not reported	Primary: At week 24, donepezil 23 mg/day provided significant cognitive benefits over 10 mg/day (P<0.01) on the SIB, with or without concomitant memantine. The higher dose showed no benefit on the global function, MMSE or ADL measures in either memantine subgroup. Rates of treatment-emergent adverse events were higher for donepezil 23 mg/day with memantine (80.7%) than 23 mg/day without memantine (69.7%) or 10 mg/day with/without memantine (66.7/62.0%); across all treatment groups, most events were mild/moderate in severity. Individual rates of serious adverse events were low (<1.0%), regardless of concomitant memantine use.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Raskind et al.[36] (2004) Galantamine 24 mg/day	OL Patients with mild-to-moderate Alzheimer's disease	N=194 36 months	Primary: ADAS-Cog, adverse events Secondary: Not reported	Primary: Patients treated continuously with galantamine for 36 months increased a mean of 10.2±0.9 points on the ADAS-Cog. This was a substantially smaller cognitive decline (approximately 50%) than that predicted for the placebo group. Patients discontinuing galantamine therapy before 36 months had declined at a similar rate before discontinuation as those completing 36 months of treatment. Almost 80% of patients who received galantamine for 36 months seemed to demonstrate cognitive benefits compared to those predicted for untreated patients. Secondary: Not reported
Rockwood et al.[37] (2008) Galantamine 24 mg/day	MC, OL Patients with Alzheimer's disease who had received galantamine treatment for up to 36 months	N=240 Up to 48 months	Primary: ADAS-Cog, DAD, adverse events Secondary: Not reported	Primary: Mean ADAS-Cog worsened from 22.6±8.6 at baseline to 31.3±13.1 at 48 months. DAD worsened from 73.4±18.1 at baseline to 36.1±29.0 at 48 months. Fifty one patients withdrew from the study. Secondary: Not reported
Wallin et al.[38] (2011) Galantamine 24 mg/day	MC, OL, PRO Patients with Alzheimer's disease and no previous cholinesterase inhibitor therapy	N=280 36 months	Primary: MMSE, ADAS-cog, IADL, CIBIC Secondary: Subgroup analysis by K-means cluster analysis	Primary: From baseline to 36 months, MMSE decreased from 23.3 to 21.74. The MMSE score was significantly better at two months (P<0.001) and at six months (P=0.006) compared to baseline, and was stable at 12 months (P=0.616) compared to baseline. The total mean decline in MMSE score from baseline after three years of treatment was 2.6 From baseline to 36 months, ADAS-cog increased from 16.85 to 19.39.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The total change in ADAS-cog score after three years of treatment was 5.6 points above baseline values. The ADAS-cog scores at six months were not different from baseline (P=0.248), but deteriorated after that. Mean IADL scores demonstrated deteriorated at all time points compared to baseline (12.76 to 17.13). According to CIBIC scores at two months, 93% of patients remaining in the study were "improved or unchanged", at months six, 12, 24, and 36; 81, 69, 50, and 41% of the patients were "improved or unchanged", respectively. Secondary: Cluster analysis identified two response clusters. Cluster 1 included patients with low ability in ADAS-cog and IADL scores at baseline. These patients were older and less educated, but responded better at six months compared to cluster two patients. Cluster 2 patients included better ADAS-cog and IADL scores at baseline. Cluster 2 patients had a higher frequency of the APOE ε4 allele.
Brodaty et al.[39] (2006) Galantamine 2 to 50 mg/day	OL, OS, PRO Patients diagnosed with mild-to-moderately severe dementia	N=345 ITT N= 229 PP 6 month follow-up	Primary: MMSE, ADAS-Cog, CIBIC-Plus, IADL Secondary: Not reported	Primary: For the MMSE 65% of PP patients had an increased score at the three-month assessment as compared to baseline with an overall 92% response rate. 70% of PP patients had an increased score at the six-month assessment as compared to baseline with an overall 91% response rate. 44% of ITT patients had an increased score at the six-month assessment as compared to baseline (P values were not reported). For ADAS-Cog at 6 months, 86% of the PP patients and 33% of the ITT patients had a decrease in ADAS-Cog score. P value was not reported. For CIBIC-Plus at three months, 91% of PP patients were considered responders by their physicians; 28% were unchanged, 38% were minimally improved, 22% were much improved, 4% were very much improved (P values not reported). For CIBIC-Plus at six months, 86% of PP patients were considered responders by their physicians; 20% were

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				unchanged, 26% were minimally improved, 32% were much improved, 7% were very much improved. In the ITT patients, 54 % were classified as responders at six months (P values not reported). Most PP patients had no change in IADL scores at three and six months (P value not reported). Most PP patients had no change in behavior scores at three and six months (P value not reported). Secondary: Not reported
Richarz et al.[40] (2014) Galantamine 8 to 24 mg/day	OL, PRO Patients ≥45 years of age with mild to moderate Alzheimer's disease	N=75 (36 months) N=159 (24 months) N=269 (6 months) Up to 36 months	Primary: ADAS-cog/11 Secondary: Bayer-ADL, NPI, CGI-C, adverse events	Primary: Mean ADAS-cog score improved significantly during the first six months, with improvement maintained until month 12. During follow-up, mean ADAS-cog score returned to baseline levels between months 18 and 24; after 36 months, it had deteriorated (increased) by 2.87 ± 11.07 points. Secondary: Mean NPI score improved significantly in the first 12 months and worsened thereafter. In the 36-month sample, patient self-rated Bayer ADL scores remained stable until 24 months of treatment; then, a significant deterioration had occurred; a significant deterioration from baseline in caregivers' Bayer ADL scores occurred after month 12. After six months of treatment, 84% of the patients who completed the six-month observation period were considered to be improved or unchanged compared with baseline on the CGI-C. In the 36-month sample, the corresponding value was 54%. In the 36-month sample, 54 patients (72%) reported at least one treatment-emergent adverse event throughout the treatment period, with most events occurring during the first two years of treatment.
Cummings et al.[41] (2004) Galantamine 8 to 24 mg/day	DB, PC, RCT Patients with mild-moderate Alzheimer's disease	N=978 21 weeks	Primary: NPI, caregiver distress related to patients' behavior	Primary: NPI scores worsened with placebo, whereas patients treated with 16 or 24 mg/day of galantamine had no change in NPI scores. Behavioral improvement in patients symptomatic at baseline ranged from

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo			Secondary: Not reported	29 to 48%. Changes were evident in patients receiving 16 and 24 mg/day of galantamine. High-dose galantamine was associated with a significant reduction in caregiver distress. Secondary: Not reported
Scarpini et al.[42] (2011) <u>Phase 1</u> Galantamine 8 to 16 mg/day <u>Phase 2</u> Galantamine 16 mg/day vs placebo	<u>Phase 1</u> MC, OL <u>Phase 2</u> DB, MC, RCT Mild to moderate Alzheimer's disease in patients ≥50 years of age (MMSE, 11 to 24)	N=393 36 months	Primary: ADAS-cog/11 deterioration ≥4 points Secondary: CIBIC-plus, adverse events	<u>Phase1</u> Primary: Cognitive functions improved significantly on the ADAS-cog/11 scale with galantamine treatment at month seven relative to baseline (from 24.1 to 22.9, difference, -1.2; 95% CI, -2.3 to -0.1; P<0.01). Scores were similar to baseline values at the end of the OL phase at month 12 (mean score at baseline, 24.1; mean score at month 12, 24.7; 95% CI, -0.5 to 1.7, P=0.16). Secondary: CIBIC-plus score improved in 34.3%, was unchanged in 30.9%, and worsened in 34.9% of patients when compared to baseline. A total of 50.4% of patients reported adverse events, of which the most common was gastrointestinal disorders (21.3%), nervous system disorders (9.8%), and psychiatric disorders (19.7%). Serious adverse events were reported in 12.2%. <u>Phase 2</u> Primary: Patients receiving placebo were more likely to discontinue therapy prematurely compared to galantamine for any reason (HR, 1.76; 95% CI, 1.10 to 2.81; P=0.02) or lack of efficacy (HR, 1.80; 95% CI, 1.02 to 3.18; P=0.04). No significant difference was observed by ADAS-cog >4 between the groups (HR, 1.66; 95% CI, 0.78 to 3.54; P=0.19). Secondary: There were no significant differences between the treatment groups concerning mean values of the CIBIC-plus scale.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				A total of 34.1% of patients receiving galantamine and 27% of patients receiving placebo experienced adverse events. The most common adverse events were nervous system disorders (6.6%) and psychiatric disorders (5.3%). Serious adverse events were reported in 14.5% of galantamine-treated patients compared to 6.3% of patients in the placebo group.
Kavanagh et al.[43] (2011) Galantamine 16 to 24 mg/day vs placebo	OL, RCT Patients with mild-to-moderate Alzheimer's disease	N=3,523 (5 trials) 5 to 6 months	Primary: Changes from baseline in ADAS-Cog 11 at trial endpoint (two to five months after reaching maintenance doses) Secondary: Not reported	Primary: The proportion of patients who met criteria for "improved", "stable", or "non-rapid decline" at trial endpoint were 45.8, 59.5, and 87.6%, respectively with galantamine compared to 27.2, 37.1, and 67.7%, respectively with placebo. Changes in ADAS-Cog 11 scores with galantamine were -4.9, -4.7, and -2.9 points, respectively, for "improved", "stable" and "non-rapid decline" compared to -3.6, -3.4, and -1.2, respectively with placebo. Patients receiving galantamine who were reported to be "improved" or "stable" experienced improvement in ADAS-Cog 11 scores until 18 months after starting treatment, and attenuated deterioration thereafter. For galantamine-treated patients exhibiting "non-rapid decline", mean ADAS-Cog 11 score returned to baseline after approximately 12 months. Secondary: Not reported
Burns et al.[44] (2009) Galantamine 24 mg/day vs placebo	DB, MC, PC, RCT Patients 40 to 95 years of age with severe dementia of the Alzheimer type or probable Alzheimer's disease (MMSE, 5 to 12 points)	N=407 6 months	Primary: SIB, MDS-ADL, and adverse events Secondary: Not reported	Primary: In the completer analysis, the mean total SIB score of the galantamine group increased to 69.1 points at week 26. The mean SIB score in the placebo group decreased to 66.9. The between group least squares mean difference was 4.36 (95% CI, 1.3 to 7.5; P=0.006). In the completer analysis, the mean total MDS-ADL self-performance score worsened in both groups: scores at week 26 were 13.0 points in the galantamine group and 13.6 points in the placebo group. The between-group least squares mean difference was –0.41 points (95% CI, –1.3 to 0.5; P=0.383). In the LOCF analysis, the mean SIB score in the galantamine group

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				increased to 69.3 points. In the placebo group, the mean SIB score decreased by 3.2 points. The between-group least squares mean difference was 5.02 points (95% CI, 2.17 to 7.86; P=0.0006). In the LOCF analysis, the mean total seven-item MDS-ADL self-performance score in the galantamine group worsened at endpoint to 13.1 points and to 14.0 points in the placebo group. Changes from baseline in the seven-item MDS-ADL self-performance score were 1.3 points and 1.7 points, respectively. The between-group least squares mean difference was –0.50 (95% CI, –1.39 to 0.39; P=0.394). Significant between-group differences were seen in the galantamine group for memory (P=0.006), praxis (P=0.010), and visuospatial ability (P=0.002). There were no significant differences in language (P=0.064) or attention (P=0.075). Scores for all eleven-item MDS-ADL self-performance subscales worsened in both treatment arms. The deterioration in the subscale score for locomotion on unit was significantly less in the galantamine group (P=0.021). During the study, 88% of patients who received galantamine and 89% who received placebo had at least one adverse event. The most common adverse events in both treatment groups were urinary tract infections, vomiting, diarrhea, nausea, and falls. Secondary: Not reported
Raskind et al.[45] (2004) Galantamine 24 mg/day vs placebo	DB, PC, RCT Patients with mild-moderate Alzheimer's disease	N=194 36 months	Primary: ADAS-Cog, adverse events Secondary: Not reported	Primary: Patients treated continuously with galantamine for 36 months increased a mean of 10.2±0.9 points on the ADAS-Cog. This was a substantially smaller cognitive decline (approximately 50%) than that predicted for the placebo group. Patients discontinuing galantamine therapy before 36 months had declined at a similar rate before discontinuation as those completing 36 months of treatment.

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				Almost 80% of patients who received galantamine for 36 months seemed to demonstrate cognitive benefits compared to those predicted for untreated patients. Secondary: Not reported
Wilcock et al.[46] (2000) Galantamine 24 mg/day vs galantamine 32 mg/day vs placebo	DB Patients with mild-moderate Alzheimer's disease	N=653 6 months	Primary: ADAS-Cog, adverse events Secondary: Not reported	Primary: Both doses of galantamine were statistically better than placebo in the mean change in ADAS-Cog from baseline to endpoint (P<0.0001). Patients taking galantamine 24 mg had a -0.5 point mean change on the ADAS-Cog scale, while the 32 mg group had a -0.8 change. This compares to a +2.4 change for the placebo group. Statistical comparisons between the 24 mg group and the 32 mg group were not conducted. Discontinuations due to adverse events were 9, 14 and 22% in the placebo, 24 and 32 mg dose groups, respectively. Secondary: Not reported
Dunbar et al.[47] (2006) Galantamine IR 8 to 16 or 24 mg/day vs galantamine ER 8 to 16 or 24 mg/day vs placebo	Post hoc analysis, DB, MC, PC, RCT Patients with mild-to-moderate probable Alzheimer's disease	N=965 7 months	Primary: Nausea and vomiting Secondary: Not reported	Primary: Nausea reports were as follows: 16.9% of the galantamine ER group, 13.8% of galantamine IR group and 5.0% of placebo group. Vomiting reports were as follows: 6.6% of the galantamine ER groups, 8.6% of the galantamine IR group and 2.2% of the placebo group. During dose titration, the area under the curve of daily percentage of patients reporting nausea or vomiting was significantly higher in the galantamine IR group compared to placebo (320.9 vs 102.9; P=0.01) but for galantamine ER vs placebo and galantamine ER vs galantamine IR no significant differences were seen ([173.5 vs 102.9; P=NS], [320.9 vs 173.5; P=NS]). The mean daily nausea rate and the mean daily vomiting rate for galantamine ER and galantamine IR were not significantly different but

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				when both were compared to placebo, significance was seen (P<0.05). The galantamine IR had a greater mean percentage of days with nausea compared to galantamine ER (38 vs 18.4%; P=0.014) while there was no significance for both galantamine groups compared to placebo. Secondary: Not reported
Brodaty et al.[48] (2005) Galantamine IR 8 to 16 or 24 mg/day vs galantamine ER 8 to 16 or 24 mg/day vs placebo	AC, DB, MC, PC, PG, RCT Patients with mild-to-moderate probable Alzheimer's disease	N=971 6 months	Primary: ADAS-cog/11, CIBIC-Plus Secondary: ADCS-ADL, NPI, ADAS-cog/13, nonmemory ADAS-cog/ memory, ADAS-Cog	Primary: Compared to placebo, galantamine was significantly more effective with improvement from baseline in ADAS-cog/11 scores (mean change, 1.3 and -1.4, respectively; P<0.001; 95% CI, –3.74 to –1.68; LOCF mean change, 1.2 and -1.3, respectively; P<0.001; 95% CI, –3.34 to –1.49). Galantamine also showed similar results when compared to placebo (OC mean change, –1.8 and 1.3, respectively; P<0.001; 95% CI, –4.17 to –2.08; LOCF mean change, –1.6 and 1.2, respectively; P<0.01; 95% CI, –3.70 to –1.86). Secondary: ADCS-ADL scores were significantly improved in the galantamine group vs placebo (P=0.003; 95% CI, 0.85 to 4.03; LOCF; P<0.001; 95% CI, 1.09 to 3.91). In galantamine groups vs placebo, NPI scores were not statistically significant but instead numerically significant (P=0.451; 95% CI, –2.77 to 1.23; LOCF; P=0.941; 95% CI, –1.85 to 1.82), (OC; P<0.205; 95% CI, –3.31 to 0.71; LOCF; P<0.102; 95% CI, –3.42 to 0.23). Statistical significance was found in cognition improvement from baseline for both galantamine groups compared to placebo based on ADAS-cog/13, non-memory ADAS-Cog, and memory ADAS-Cog scores.
Loy et al.[49] (2006) Galantamine 8 to 36 mg/day	MA (10 trials) Patients diagnosed with mild cognitive impairment or	N=6,805 12 weeks-2 years	Primary: CIBIC-plus, ADAS-Cog, ADCS-ADL, DAD, NPI	Primary: Statistically significant difference was seen on the global rating scales for patients treated with galantamine, at all durations and all doses but 8 mg/day (P values varied).

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vs placebo	Alzheimer's disease		Secondary: Not reported	Statistically significant difference was seen on the ADAS-Cog scale for patients treated with galantamine at all doses, with greater effect at six months than three months (P values varied). When reported, ADCS-ADL, DAD, and NPI scores for patients treated with galantamine were significantly improved over those in the placebo group (P values not reported). Secondary: Not reported
Herrmann et al.[50] (2011) Memantine 20 mg/day	OL Patients with moderate-to-severe Alzheimer's disease	N=31 3 months	Primary NPI-NH change in agitation and aggression subscale, CGI-C scale, caregiver impact, and effect on nursing burden measured by M-NCAS Secondary: Caregiver distress subscale of the NPI-NH, changes in psychotropic medications	Primary: There was a significant decrease in the NPI-NH agitation/aggression subscale score with memantine (P=0.014). According to the CGI-C scores, 48% of patients were improved (much improved or minimally improved). A total of 52% of patients did not benefit from treatment (no change, minimally worse or much worse). There was a significant decrease in the M-NCAS total score (P=0.005), as well as decreases on the attitude (P=0.009) and strain (P=0.013) subscales with memantine therapy. Secondary: The NPI-NH subscale score decreased significantly with memantine therapy (P=0.009). Psychotropic medications were available in 28 patients, with 64.3% receiving at least one dose during the study. Lorazepam was the most commonly used psychotropic (P=0.046). Overall, seven patients decreased psychotropic medication use during the study, while three increased usage; Most remained the same for psychotropic usage.
Bakchine et al.[51] (2007) Memantine 20 mg/day	DB, PC Patients with mild-to-moderate Alzheimer's disease	N=470 24 weeks	Primary: ADAS-COG and CIBIC-plus Secondary: Not reported	Primary: Patients in the memantine group showed a statistically significant improvement relative to placebo in ADAS-COG and CIBIC-plus at weeks 12 and 18. There was no significant difference between the groups at week 24.

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vs placebo				Secondary: Not reported
Reisberg et al.[52] (2003) Memantine 20 mg/day vs placebo	DB, PG Patients with moderate-to-severe Alzheimer's disease	N=252 28 weeks	Primary: CIBIC-Plus and ADCS-ADL Secondary: SIB	Primary: A significantly greater effect was observed in the memantine group compared to the placebo group on the ADCS-ADL (P=0.03). There was a significant difference in favor of memantine at week 28 on the CIBIC-Plus using the observed-cases analysis (mean score, 4.7 placebo vs 4.4, memantine; P=0.03), and a numerical difference at study endpoint in favor of memantine using the last-observed-carried-forward analysis (mean score, 4.8 placebo vs 4.5 memantine; P=0.06). Secondary: Memantine patients showed significantly less cognitive decline on the SIB total score compared to placebo-treated patients over the 28-week study period (P=0.002).
Winblad et al.[53] (1999) Memantine 10 mg/day vs placebo	DB, PC Patients in Latvia with severe dementia, either Alzheimer's disease or vascular dementia	N=166 12 weeks	Primary: CGI-C and BGP Secondary: Safety	Primary: Significantly greater improvement was observed in the memantine group compared to the placebo group on the BGP and the CGI-C (P<0.016 and P<0.001, respectively). Separate analyses of the Alzheimer's disease population alone also yielded statistically significant results in favor of patients receiving memantine, by either the last-observed-carried-forward analysis or the observed-cases analysis on both outcome measures. At study endpoint, memantine patients showed significantly greater functional improvement compared to patients who received placebo, at study endpoint (P=0.012). Secondary: No significant differences in safety were found between the groups.
Winblad et al.[54] (2007) Memantine 20	MA Four studies: memantine as	N=1,826 in subgroup with moderate-to-	Primary: CIBIC-Plus, SIB, ADAS-Cog, ADCS-ADL, NPI	Primary: There was a statistically significant advantage for the memantine group over the placebo group in all 4 efficacy domains: CIBIC-Plus or global status (P<0.001), SIB or ADAS-Cog status (P<0.001), ADCS-ADL

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mg/day vs placebo	monotherapy, 2 studies of memantine vs placebo in patients already taking an acetylcholinesterase inhibitor; patients diagnosed with moderate-to-severe Alzheimer's disease	severe Alzheimer's disease 24 to 28 weeks	Secondary: Not reported	(P<0.001) and NPI (P=0.03). Secondary: Not reported
Wilkinson et al.[55] (2007) Memantine 20 mg/day vs placebo	MA Patients diagnosed with moderate-to-severe Alzheimer's disease	N=1,826 24 to 28 weeks	Primary: ADAS-Cog, SIB, CIBIC-Pus, ADCS-ADL Secondary: Not reported	Primary: Significantly more patients in the placebo group (21%) had marked clinical worsening, as demonstrated by deteriorating scores, than in the memantine group (11%; P<0.001). Significantly more patients in the placebo group (28%) compared to the memantine group (18%) had documentation of worsening in any outcome measure (P<0.001). Secondary: Not reported
McShane et al.[56] (2006) Memantine 10 to 30 mg/day vs placebo	MA (12 trials) Patients diagnosed with mild-to-moderate, moderate-to-severe and mild-to-moderate vascular dementia	N=3,731 (15 trials) Variable duration	Primary: CIBIC-Plus, SIB, ADAS-Cog, ADCS-ADL, NPI Secondary: Not reported	Primary: Significant improvement at six months was seen for patients with mild-to-moderate dementia treated with memantine on the ADAS-Cog scale (P=0.03); however, there was no significant difference seen for behavior and ADL scales. Significant improvement at six months was seen for patients with moderate-to-severe dementia treated with memantine for the following scales: CIBIC-Plus (P<0.00001), SIB (P<0.00001), ADCS-ADL (P=0.003) and NPI (P=0.004). Patients with vascular dementia treated with memantine had significant improvement in cognition scores and behavior scores but no significant change in global rating scales (ADAS-Cog; P=0.0002, NPI; P=0.03). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Grossberg et al.[57] (2013) Memantine extended-release 28 mg once daily vs placebo	DB, MC, RCT Outpatients with Alzheimer's disease (MMSE scores of three to 14) who were receiving stable, ongoing cholinesterase inhibitor treatment	N=677 24 weeks	Primary: Baseline-to-endpoint score change on the SIB and the endpoint score on the CIBIC-Plus Secondary: Baseline-to-endpoint score change on the ADCS-ADL19; additional parameters included the baseline-to-endpoint score changes on the NPI and verbal fluency test	Primary: At 24 weeks memantine-treated patients significantly outperformed placebo-treated patients on the SIB (2.6; 95% CI, 1.0 to 4.2; P=0.001) and CIBIC-Plus (P=0.008). Secondary: At 24 weeks memantine-treated patients significantly outperformed placebo-treated patients on the NPI (P=0.005), and verbal fluency test (P=0.004); the effect did not achieve significance on ADCS-ADL19 (P=0.177). Adverse events with a frequency of >5.0 % that were more prevalent in the memantine group were headache (5.6 vs 5.1 %) and diarrhea (5.0 vs 3.9 %).
Grossberg et al.[58] (2018) Memantine extended-release 28 mg once daily vs placebo	Post-hoc analysis of DB, RCT Outpatients with Alzheimer's disease (MMSE scores of three to 14) who were receiving stable, ongoing cholinesterase inhibitor (ChEI) treatment	N=677 24 weeks	Primary: Comparing patients receiving memantine ER/ cholinesterase inhibitor (ChEI) to placebo/ChEI for time to onset of response and if the response was maintained (achieving improvement at weeks eight, 12, or 18 and maintaining through	Primary: Greater percentages of memantine ER/ChEI patients achieved an early response that was maintained on SIB, NPI, and CIBIC-Plus (P<0.05) versus placebo/ChEI. Greater percentages of memantine ER/ChEI-treated patients achieved and maintained a clinically notable response on ADL/NPI, SIB/ADL/NPI, and SIB/ADL/CIBIC-Plus, compared with placebo/ChEI (P<0.05). Memantine ER results in early, maintained improvement in patients with moderate to severe Alzheimer's disease concurrently taking ChEIs, compared with cholinesterase treatment alone. Secondary: When comparing memantine ER/ChEI-treated versus placebo/ChEI-treated responders for all possible combinations of two, three, or four efficacy measures, a greater proportion of memantine ER/ChEI patients showed no decline and clinically notable response versus ChEI alone. The difference between treatments for patients who showed no decline did not

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			endpoint/week 24) Secondary: Comparing percentages of patients for all possible combinations of two to four assessments with either no decline or clinically notable response	reach statistical significance; the combination of efficacy outcomes with the greatest difference was SIB/CIBIC-Plus (P=0.0541).
Hager et al.[59] (2016) Galantamine vs placebo Memantine was taken at baseline and throughout the study by 24.5% of galantamine-treated patients and 24.0% of placebo-treated patients	Post-hoc analysis of DB, PC, PRO, RCT Patients with mild-to-moderate Alzheimer's disease or mixed dementia stratified by the presence or absence of concomitant memantine	N=2,045 2 years	Primary: Mortality and efficacy parameters including MMSE scores, DAD scores, and nursing home placement Secondary: Not reported	Primary: In memantine users, mortality rates were not reduced by galantamine (HR, 1.25; 95% CI, 0.63 to 2.46) as they were in nonusers (HR, 0.33; 95% CI, 0.18 to 0.61). Mortality rates in the galantamine-treated groups, compared with placebo, were lower in patient groups with ≥ median age and higher MMSE score (18 to 26). In memantine users, galantamine did not reduce MMSE decline at any time point. In contrast, in memantine nonusers the galantamine group showed reduced decline in MMSE scores as compared with the placebo group at all time points, with a numerical increase in the effect size over time (P>0.05 for all comparisons). Examination of DAD scores at month 24 demonstrated a benefit in galantamine-treated memantine nonusers, with attenuation of this benefit in the memantine user group across the range of baseline MMSE scores. In memantine users, the risk of new nursing home admission during year one was higher in the galantamine group than in the placebo group (3.70; 95% CI, 1.04 to 13.23; P=0.03). In memantine nonusers, the risk of nursing home placement tended to be lower in galantamine-treated patients than in placebo-treated patients in year two (RR, 0.19; 95% CI, 0.02 to 1.57; P=0.08). The cumulative numerical percentages of nursing home placements were 5.0% and 18.8% in memantine users on placebo

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				and galantamine, respectively, and 5.0% and 1.8% in memantine nonusers on placebo and galantamine. Overall, the beneficial effects of galantamine at two years post treatment were not observed in patients who had been placed on background memantine. Secondary: Not reported
Burns et al.[60] (2004) Rivastigmine	RETRO Patients with moderately severe Alzheimer's disease/dementia	N=2,126 3 trials, each 6 months	Primary: Effectiveness Secondary: Not reported	Primary: Mean ADAS-Cog score declined by 6.3 points in the placebo group and increased by 0.2 points in the rivastigmine group (P<0.001). Clinical benefits were also observed with the MMSE, the six-item PDS, and items of the BEHAV-AD assessed efficacy. Rivastigmine showed the same pattern of adverse events as in other studies, but the RR of dropping out due to adverse events was lower than in subjects with milder Alzheimer's disease. Secondary: Not reported
Dantoine et al.[61] (2006) Rivastigmine 3 to 12 mg/day Addition of memantine 5 to 20 mg/day was allowed for non-responders of rivastigmine at the end of week 16.	MC, OL Patients at least 50 years of age with probable Alzheimer's disease according to criteria of DSM-IV, baseline scores of <18 for MMSE or scores of >4 on GDS, previously treated for at least 6 months prior with donepezil 5 to 10	N=202 16 weeks of rivastigmine monotherapy (Phase 1) Additional 12 weeks of rivastigmine and memantine combination therapy for non-	Primary: MMSE Secondary: MMSE, Mini-Zarit inventory, NPI, Ten-point Clock-drawing Test, D-KEFS verbal fluency test, CGI-C	Primary: Based on MMSE scores, 46.3% of patients improved or stabilized on rivastigmine monotherapy at the end of Phase 1. For those patients previously on donepezil or galantamine, responder rates were also similar (46.6 and 46.4%). At the end of Phase 2 with combination therapy of rivastigmine and memantine, according to MMSE scores, 77.9% of patients improved or stabilized. Patients switching to combination therapy from galantamine responded more significantly than those who switched from donepezil (84.2 vs 72.3%; P=0.047).

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	mg/day or galantamine 16 to 24 mg/day and considered not stabilized, current stabilized medications allowed	responders of rivastigmine monotherapy (Phase 2) Total 28 weeks		Secondary: According to CGI-C data, no change or improvement was seen in 76.5% of patients who completed the study at the end of Phase 1. For the 82.6% who worsened from baseline at the end of Phase 1, 81.4% improved or had no change at the end of Phase 2 with the addition of memantine on the CGI-C. At the end of Phase 1, MMSE and NPI showed significant improvements (P<0.001 and P<0.05, respectively) while there was no change from baseline for Ten-point Clock-drawing Test and D-KEFS verbal fluency test scores and the Mini-Zarit interview. At the end of Phase 2, D-KEFS verbal fluency test, Mini-Zarit, and especially MMSE scores showed significant improvement (P<0.05, P<0.001 and P<0.001, respectively).
Olin et al.[62] (2010) Rivastigmine 6 to 12 mg/day and memantine 20 mg/day	MC, OL, PRO Patients ≥50 years of age with moderate-to-severe Alzheimer's disease (MMSE ≥10 to ≤20)	N=116 26 weeks	Primary: Safety and tolerability Secondary: ADCS-CGIC, ADCS-ADL measured	Primary: Nausea and vomiting occurred in 26.7 and 10.3% of patients, respectively. Most cases were mild with few severe cases reported (2.6 and 2.6%, respectively). At least one treatment-emergent adverse event was experienced by 81.9% of patients. The most common adverse events were nausea (26.7%), dizziness (11.2%), vomiting (10.3%), and diarrhea (10.3%). No patients exhibited clinically significant ECG abnormalities. Secondary: At week 26, 59% of patients experienced no decline in MMSE total score from baseline. The mean change from baseline in MMSE total score was 0.7. At week 26, there was no change in global ADCS-CGIC scores. Patient and caregiver assessed mental/cognitive state, behavior and functioning severity scores were maintained to a similar extent throughout the study.

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				The mean overall rating on the ADCS-CGIC was 4.0. At week 26, 64.5% of patients were considered unchanged or improved. The mean ADAS-ADL scores significantly declined by -2.9. At week 26, cognition, behavior and global functioning were unchanged or improved in 63.2, 71.1 and 77.6% of patients respectively.
Gauthier et al.[63] (2010) Rivastigmine 3 to 12 mg/day	MC, OL, OS, PRO Patients with mild-moderate Alzheimer's disease	N=3,800 12 months	Primary: Physician-assessed abbreviated CGI-C, MMSE, psychotropic medication use Secondary: Not reported	Primary: At six months, the proportion of patients who were reported as being improved vs no change vs deteriorating were 46.4 vs 44.9 vs 8.8% for attention; 42.8 vs 50.0 vs 7.2% for apathy; 41.1 vs 49.5 vs 9.4% for anxiety; 33.8 vs 68.4 vs 7.7% for agitation; 35.1 vs 54.8 vs 10.1% for irritability; and 30.8 vs 63.8 vs 5.4% for sleep disturbance. At 12 months, the proportion of patients who were reported as being improved vs no change vs deteriorating were 47.9 vs 41.0 vs 11.1 for attention; 44.1 vs 46.7 vs 9.2% for apathy; 41.8 vs 47.3 vs 10.9% for anxiety; 33.5 vs 57.6 vs 8.9% for agitation; 33.8 vs 56.4 vs 9.8% for irritability; and 29.7 vs 64.7 vs 5.6% for sleep disturbance. Overall, CGI-C at six and 12 months demonstrated a larger percentage of patients with improvement vs deterioration. At six months, 54% of patients overall demonstrated no change. At 12 months, 52% of patients overall demonstrated no change. MMSE scores were 20.8 at baseline, 21.5 after three months, 21.3 after six months, and 21.3 after 12 months. At baseline, 61.3% of patients were not taking a psychotropic medication. At six months, the proportion of patients not taking any psychotropic medications increased to 70.8%; at 12 months, it was 84.7%.
Birks et al.[64] (2000) Rivastigmine 6 to 12 mg/day	MA (8 trials) Patients diagnosed with Alzheimer's disease	N=3,660 12 to 52 weeks	Primary: ADAS-Cog, ADL, adverse events Secondary:	Primary: Statistically significant differences were seen in patients treated with rivastigmine at doses of 6 to 12 mg/day as compared to placebo for the following outcomes: ADAS-Cog (WMD, -2.09; 95% CI, –2.65 to –1.54) and ADL (WMD, -2.15; 95% CI, –3.16 to –1.13).

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vs placebo			Not reported	At 26 weeks, 55% of patient had severe dementia in the rivastigmine group as compared to 59% in the placebo group (OR, 0.78; 95% CI, 0.64 to 0.94). Adverse events (nausea, vomiting, diarrhea, anorexia, headache, syncope, abdominal pain and dizziness) were reported significantly more frequently in the rivastigmine group than with placebo. Secondary: Not reported
Birks et al.[65] (2009) Rivastigmine vs placebo	MA Patients diagnosed with probable Alzheimer's disease	N=4,775 (9 trials) Variable duration	Primary: Cognitive function, global impression, activities of daily living, behavioral disturbance, withdrawal rates, and incidence of adverse effects Secondary: Not reported	Primary: <u>Cognitive function</u> The meta-analysis, using WMD, demonstrated benefit on cognitive function as measured by ADAS-Cog test scores for rivastigmine compared to placebo as follows: rivastigmine 1 to 4 mg/day at 18 weeks (WMD, -1.07; 95% CI, -1.66 to -0.48; P=0.0004) and 26 weeks (WMD, -0.84; 95% CI, -1.48 to -0.19; P=0.01); rivastigmine 6 to 12 mg/day at 12 weeks (WMD, -1.49; 95% CI, -1.96 to -1.01; P<0.00001), 18 weeks (WMD, -1.79; 95% CI, -2.30 to -1.29; P<0.00001) and 26 weeks (WMD, -1.99; 95% CI, -2.49 to -1.50; P<0.00001). An additional analysis of ADAS-Cog dichotomized into those showing less than four points improvement and those showing four or more points improvement at 26 weeks shows benefit for cognitive function for the 6 to 12 mg daily of rivastigmine compared to placebo (83% did not show four points improvement compared to 89%; OR, 0.6; 95% CI, 0.4 to 0.8). There was no difference for the 1 to 4 mg/day dose compared to placebo (88% did not show four points improvement compared to 90%; OR, 0.84; 95% CI, 0.60 to 1.19). MMSE shows similar results in favor of rivastigmine at 26 weeks compared to placebo as follows: rivastigmine 1 to 4 mg/day at 26 weeks (WMD, 0.43; 95% CI, 0.08 to 0.78; P=0.02) and rivastigmine 6 to 12 mg/day at 26 weeks (WMD, 0.82; 95% CI, 0.56 to 1.08; P<0.00001). One study used the SIB, which shows benefit associated with higher dose

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				rivastigmine compared to placebo at 26 weeks (WMD, 4.53; 95% CI, 0.47 to 8.59; P=0.03). Global assessment Using the CIBIC-Plus scale or the ADCS-CGIC scale, there were benefits associated with rivastigmine compared to placebo as follows: rivastigmine 6 to 12 mg/day at 12 weeks (OR, 0.74; 95% CI, 0.60 to 0.92; P=0.008), 18 weeks (OR, 0.79; 95% CI, 0.64 to 0.98; P=0.03) and at 26 weeks (OR, 0.66; 95% CI, 0.55 to 0.79; P<0.00001); rivastigmine 1 to 4 mg/day at 26 weeks (OR, 0.71; 95% CI, 0.55 to 0.93; P=0.01). Using GDS, there were benefits associated with rivastigmine 6 to 12 mg/day compared to placebo (55% showed the worse condition compared to 59%; OR, 0.78; 95% CI, 0.64 to 0.94; P=0.01) but not with 1 to 4 mg daily rivastigmine compared to placebo. ADL The PDS showed an improvement associated with rivastigmine compared to placebo as follows: rivastigmine 6 to 12 mg/day at 12 weeks (WMD, 1.08; 95% CI, 0.19 to 1.98; P=0.02), 18 weeks (WMD, 1.90; 95% CI, 0.93 to 2.88; P=0.0001), and 26 weeks (WMD, 2.15; 95% CI, 1.13 to 3.16; P<0.0001). One study assessing ADL using the ADCS-ADL scale and showed benefit for rivastigmine 6 to 12 mg/day at 24 weeks (WMD, 1.80; 95% CI, 0.20 to 3.40; P=0.03). Behavioral disturbance There was no difference between rivastigmine and placebo in behavioral disturbance found in two studies using the neuropsychiatric instrument (NPI-10, and NPI-12). Withdrawals before the end of treatment There were no significant differences in withdrawal rates with rivastigmine 1 to 4 mg/day and placebo at 12, 18 and 26 weeks. There were significant differences in withdrawal rates for the higher dose group in favor of placebo as follows: rivastigmine 6 to 12 mg/day at 12 weeks (OR, 2.60; 95% CI, 1.19 to 5.68; P=0.02), 18 weeks (OR, 4.02;

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				95% CI, 1.31 to 12.32; P=0.01), and 26 weeks (OR, 2.19; 95% CI, 1.83 to 2.63; P<0.00001). Adverse events There were no significant differences in the numbers of patients with at least one adverse event between the lower dose rivastigmine (1 to 4 mg/day) and placebo groups. There were significant differences between the higher dose rivastigmine (6 to 12 mg/day) and placebo groups in favor of placebo by the end of the titration period (OR, 2.96; 95% CI, 2.39 to 3.68; P<0.00001) and by 26 weeks (OR, 2.49; 95% CI, 2.05 to 3.02; P<0.00001). There were no significant differences in the numbers of patients with at least one severe adverse event between the lower dose rivastigmine (1 to 4 mg/day) and placebo groups. There were significant differences between the higher dose rivastigmine (6 to 12 mg daily) and placebo groups in favor of the placebo group for the titration period (OR, 1.88; 95% CI, 1.39 to 2.55; P<0.0001). There were significant differences, in favor of placebo, for the rivastigmine 6 to 12 mg/day group by the end of the titration period, and by 26 weeks for the number of patients suffering nausea, vomiting, diarrhea, anorexia, headache, syncope, abdominal pain and dizziness. There were significant differences in favor of placebo, for the rivastigmine 1 to 4 mg/day group by the end of the titration period and by 26 weeks for the number of patients suffering nausea, vomiting, diarrhea, and anorexia. Secondary: Not reported
Rosler et al.[66] (1999) Rivastigmine 1 to 4 mg/day vs	DB, MC, PC, RCT Patients 50 to 85 years of age and not able to bear children, all patients met criteria for Alzheimer's type	N=725 Dose titration over the first 12 weeks with a subsequent assessment	Primary: Improvements in cognitive function and overall clinical status measured by the ADAS-Cog, CIBIC, PDS, MMSE and GDS	Primary: Significant improvement in cognitive function assessed by the ADAS-Cog was observed with the higher dose group by ≥4 points compared to placebo (P<0.05). At week 26, significantly more patients in both rivastigmine groups had improved in global function as assessed by the CIBIC compared to those in the placebo group (P<0.05).

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rivastigmine 6 to 12 mg/day vs placebo	dementia as described in the DSM-IV and criteria for probable Alzheimer's disease	period of 14 weeks, total of 26 weeks	Secondary: Safety and tolerability	Mean scores on the PDS improved from baseline in the higher dose group but fell in the placebo group (P<0.05). At week 26, mean scores in the MMSE and the GDS significantly improved in patients receiving rivastigmine 6 to 12 mg/day (P<0.05). Secondary: Discontinuation rates for any reason were significantly higher in the higher dose group than in the lower dose or placebo group (33% vs 14%). Adverse events related to treatment including nausea, vomiting, diarrhea, abdominal pain and anorexia, were generally mild and occurred most frequently during the dose escalation phase (23% in higher dose group, 7% in lower dose group and 7% in placebo group).
Articus et al.[67] (2011) Rivastigmine patch 9.5 mg/24 hours	MC, OL Patients with Alzheimer's disease	N=208 24 weeks	Primary: Proportion of patients treated with rivastigmine for ≥8 weeks at week 24 Secondary: Tolerability, week 24 MMSE, ADCS-CGIC, ADCS-ADL, ADCPQ, Zarit Burden Interview Score	Primary: In the ITT population, 80.8% of patients (95% CI, 75.0 to 86.5) were treated for at least eight weeks with rivastigmine. A total of 74.2% of patients (95% CI, 67.8 to 80.5) were treated for at least eight weeks and completed the study. A total of 74.2% of patients treated rivastigmine patch were able to reach and maintain the maximum dose for at least eight weeks. The most common adverse events being nausea (10.1%), erythema (8.7%), pruritus (8.2%), and vomiting (7.2%). Secondary: The most common adverse events were nausea (10.1%), erythema (8.7%), pruritus (8.2%), vomiting (7.2%), diarrhea (4.3%) and agitation (4.3%). At week 24, improvements were seen on: MMSE (1.3), and ADCS-ADL (1.3). At week 24, improvements in ADCS-CGIC were demonstrated in 34.6% of patients as assessed by patients, and in 29.7% of patients as assessed by the caregiver.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				ADCPQ scores improved 18.5 points, and Zarit Burden Interview Score improved slightly at each visit until week 24 (-0.4).
Grossberg et al.[68] (2009) Rivastigmine patch 9.5 mg/24 hours to 17.4 mg/24 hours	OL Patients 50 to 85 years of age with Alzheimer's disease (MMSE scores 10 to 20)	N=870 28 weeks (weeks 25 to 52 of open-label extension)	Primary: Safety and tolerability Secondary: ADAS-cog	Primary: During the first four weeks of the open-label extension, patients formerly randomized to rivastigmine treatment (capsule or patch) reported fewer adverse events than those formerly randomized to placebo (≤15.2 vs 28.2%). This prior exposure effect was noted for nausea (≤2.5 vs 8.5%) and vomiting (≤1.9 vs 6.0%). A total of 57.6% of patients reported adverse events during the OL extension (weeks 25 to 52), with nausea and vomiting being reported most frequently (15.7 and 14.3%, respectively). During the OL extension, over 90% of all patients experienced ''no, slight, or mild'' skin irritation as their most severe application-site reaction. The symptoms that were most commonly reported as moderate or severe were erythema and pruritus (7.7 and 5.6%, respectively). Serious adverse events occurred in 1.0% of patients during the first four weeks of the OL extension phase (weeks 25 to 28) and 9.4% of patients during the full open-label extension phase (weeks 25 to 52). The most common serious adverse events were gastrointestinal disorders (2.0%), infections and infestations (2.0%), cardiac disorders (1.7%), and nervous system disorders (1.5%). Eight deaths occurred during the OL extension phase and a further two occurred during the 30-day follow-up period. The causes of death were most commonly cardiac disorders (n=5) and nervous system disorders (n=3). None were considered treatment related. Secondary: Patients previously randomized to placebo who were switched to the 9.5 mg/24 hour rivastigmine patch during the OL extension experienced a 1.3-point increase in their ADAS-cog scores during weeks 24 to 40. There was no overall change in ADAS-cog score at week 40 compared to baseline (95% CI, -1.4 to 0.6). The increase in ADAS-cog score was not sustained beyond week 40.

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				Patients receiving rivastigmine treatment for the entire study (weeks 0 to 52) showed a deterioration of 0.3 points (95% CI, -0.4 to 0.9) on the ADAS-cog at week 52. Those receiving placebo for weeks 0 to 24, followed by the patch, showed a deterioration of 0.9 points [95% CI, -0.4 to 2.1).
Gauthier et al.[69] (2013) Rivastigmine transdermal patch 4.6 mg/24 hours or 9.5 mg/24 hours, once daily	OS Patients with Alzheimer's disease with MMSE score of 10 to 26 and GDS score of 4 to 6	N=1,204 18 months	Primary: Change in MMSE from baseline to 18 months Secondary: Change in MMSE at six and 12 months and change in GDS, assessment of patient ability, overall patient assessment rating, caregiver-reported compliance and treatment satisfaction at six, 12, and 18 months	Primary: Over 18 months of treatment there were no clinically significant changes in MMSE. Secondary: Over 18 months of treatment there were no clinically significant changes in GDS. The majority of patients showed improvement or no change in GDS, assessment of patient ability and overall patient assessment rating over 18 months. The proportion with reported improvement in GDS, assessment of patient ability and overall patient assessment rating was higher than the proportion that deteriorated. Compliance improved from baseline to 18 months and for 88.2% of patient's caregivers preferred the transdermal patch to oral medications.
Sadowsky et al.[70] (2010) US13 and US18 Rivastigmine capsules 3 to 12 mg/day US38 Rivastigmine patch 4.6 mg/24 hours for 5 weeks, then rivastigmine patch	US13 and US18 PRO, MC, OL US38 RCT, MC, OL Patients ≥49 years of age with a diagnosis of dementia of the Alzheimer type (MMSE ≥8 to ≤26 or MMSE ≥10 to	N=592 25 to 26 weeks	Primary: Safety and tolerability	Primary: In US13 and US18, 67.7% of patients completed the studies and 32.3% of patients withdrew due to adverse events (59.8%), unsatisfactory treatment effect (15.9%), withdrawal of consent (15%), and loss to follow-up (6.5%). The remaining 2.7% of patients discontinued due to protocol deviation, administrative problem, or death. In US13 and US18, the most frequently reported adverse events (AEs) were nausea (32.9%), vomiting (24.1%), dizziness (11.8%), weight loss (9.1%) agitation (7.9%), fall (7.9%) and confused state (7.9%). Serious AE's were reported in 6% of patients and included pneumonia (1.8%), syncope (1.2%), dehydration (1.2%) and vomiting (1.2%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
9.5 mg/24 hours for 20 weeks	≤24) who showed a poor response to donepezil			In US38, 67.4% of patients completed the study. The primary reasons for not completing the study were adverse events (44.7%), withdrawal of consent (29.4%), unsatisfactory treatment effect (10.6%), protocol deviation (7.1%), and loss to follow-up (3.5%). The remaining 4.7% of patients discontinued due to administrative problems, abnormal test procedure, or death. In US38, 70.5% of patients reported at least 1 AE. More patients in the immediate-switch group (73.3%) experienced at least one AE during the study than in the delayed-switch group (67.7%). The most common adverse events were application site reaction (15.3%), and agitation (6.9%). The most common serious AEs reported were syncope (1.1%), dehydration (0.8%) and pneumonia (0.4%). Discontinuation due to AE (14.6%) was the most common reason for patients not completing the extension phase in both immediate- and delayed-switch groups; the differences between the groups were NS. Discontinuations occurred for the following reasons: application site reaction (4.2%), disease progression (2.3%), and agitation (1.5%). Discontinuation due to gastrointestinal AEs was lower for the rivastigmine patch compared to the capsules.
Cummings et al.[71] (2012) 10 cm^2 rivastigmine patch (9.5 mg/24 hours) vs 15 cm^2 rivastigmine patch (13.3 mg/24 hours)	DB, PG. RCT Patients 50 to 85 years of age with MMSE scores of 10 to 24 diagnosed with Alzheimer's disease, all patients were required to be living with someone or to be in daily contact with a caregiver	N=567 48 weeks	Primary: ADCS-IADL scale and ADAS-cog Secondary: Time to functional decline on the ADCS-IADL, change in the Trail Making Test parts A and B, and change in the NPI-10, and the NPI-caregiver distress scale.	Primary: The 13.3 mg/24 hours patch was statistically superior to the 9.5 mg/24 hours patch on the ADCS-IADL scale from week 16 (P=0.025) onwards including week 48 (P = 0.002), and ADAS-cog at week 24 (P= 0.027), but not at week 48 (P = 0.227). Secondary: Functional decline on the ADCS-IADL tended to occur later in the 13.3 mg/24 h patch group than in the 9.5 mg/24 hours patch group, but the observed difference did not reach significance. Proportion of patients with functional decline was 77.0% in the 13.3 mg/24 hours patch group compared to 81.2% with the 9.5 mg/24 hours patch Group. The difference was not statistically significant. Patients in the 13.3 mg/24 hours patch group had smaller increases in time

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				to complete the Trail Making Test parts A at weeks 24 and 48 compared to those in the 9.5 mg/24 hours patch group, but the observed difference did not reach significance. Differences were not significantly different in changes in the change in the 10-item (NPI-10), and the NPI-caregiver distress scale. The most frequently reported adverse events by primary system organ class were gastrointestinal disorders (29.3 vs. 19.1%, 13.3 and 9.5 mg/24 hours patch, respectively), psychiatric disorders (25.4 vs. 21.6%, respectively) and nervous system disorders (21.4 vs. 18.4%, respectively). Skin and subcutaneous tissue disorders were less frequently observed with the 13.3 mg/24 hours than the 9.5 mg/24 hours patch (2.1 vs 6%).
Cummings et al.[72] (2010) Rivastigmine patch 9.5 mg/24 hours vs rivastigmine patch 17.4 mg/24 hours vs placebo	DB, PC, PRO, RCT Patients 50 to 85 years of age with mild-to-moderate Alzheimer's disease	N=1,195 24 to 52 weeks	Primary: Tolerability at 24 weeks Secondary: Patients skin condition at the application site at 28 weeks	Primary: No serious skin reactions were reported in either the 24 or 28 week phases of the study. During the 24 week period, 574 patients wearing an active patch and 579 patients wearing a placebo patch underwent at least one assessment of application-site skin condition. Of patients on the 9.5 mg/24 hour patch, erythema and pruritus were the most commonly reported reactions (moderate in 7.6% of patients and severe in 6.7% of patients). A total of 89.6% of patients in the patch group had "no, slight, or mild" signs and symptoms for their most severe application site reaction. Secondary: A total of 870 patients entered the 28 week phase of the study and received rivastigmine 9.5 mg/24 hours patch. Overall, the skin tolerability profile was similar to the DB phase. A total of 91.5% of patients experienced "no, slight, or mild" symptoms as their most severe application site reaction, with erythema and pruritus being the most common finding. A total of 3.7% of patients discontinued treatment due to skin reactions during the open-label extension, and there was no increase in the severity of skin reaction noted.
Molinuevo et al.[73] (2012)	MC, OS, PRO	N=649	Primary: Adherence rates	Primary: At baseline, 0.6% of patients were taking ≥80% of their medication as

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rivastigmine patch 9.5 mg/24 hours vs rivastigmine 3 to 12 mg/day	Patients with mild-to-moderate Alzheimer's disease	6 months	Secondary: Strategies followed by a physician to improve adherence and reasons for nonadherence reported by patients	prescribed. At three and six months, 77 and 88.1%, respectively, were noted to be taking more than 80% of their medication as prescribed (P<0.0001 vs baseline). The proportion of adherent patients at three months was 73.6% and at six months was 85.9% (P<0.0001). Secondary: Modification of Alzheimer's disease treatment was the only intervention that substantially improved adherence at three months (P<0.0001). At the six month visit, psychoeducation was the only effective strategy that reached statistical significance (P<0.0001). The most common reasons for nonadherence include forgetfulness (56.4%), avoidance of adverse events (30.7%), and refusal of treatment (25.3%).
Boada et al.[74] (2013) Rivastigmine transdermal patch vs rivastigmine capsules	OL Patients treated with rivastigmine	N=1,078 Duration not specified	Primary: Patient satisfaction (Treatment Satisfaction with Medicines and the Morisky-Green questionnaires) Secondary: Not reported	Primary: Satisfaction reported was greater with transdermal than oral rivastigmine: mean+standard deviation of the total Treatment Satisfaction with Medicines score, 72.5+14.1 vs 65.2+12.5; P<0.001. The proportion of adherent patients was greater with transdermal than with oral rivastigmine (65.0 vs 41.4%; P<0.001). Satisfaction, in turn, was significantly greater in adherent cases than in nonadherent cases. Secondary: Not reported
Blesa González et al.[75] (2011) Rivastigmine 6 to 12 mg/day (RO) vs rivastigmine patch	MC, OL, RCT Patients ≥60 years of age with mild-to-moderate Alzheimer's disease who were previously treated with oral rivastigmine	N=142 3 months	Primary: Gastrointestinal adverse events Secondary: Overall tolerance, local tolerance for those patients on patches, satisfaction level, and cognitive	Primary: Gastrointestinal adverse events were reported in <5% of patients receiving patches (4.7% in RPT and 4.3% in RP) vs 6.1% in RO patients. No statistical significance was reached (P=0.8667). Gastrointestinal adverse events were noted in 11 cases, two in RPT patients, six in RP patients, and three in the RO patients (P=0.3067). Secondary: Overall tolerability did not reveal any significant differences among the groups (P=0.8239).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
titrated to 9.5 mg/24 hours (RPT) vs rivastigmine patch 9.5 mg/24 hours (RP)			state by MMSE	Local tolerability revealed skin or subcutaneous tissue adverse events reported in 11.6% of patients in the RPT group vs 17% of patients in the RP group (P=0.4055). All skin adverse events were reported as slight or moderate intensity. RP was defined by 72% of patients as very easy to use, while RO was considered very easy to use by 30% of patients (P=0.0005). In RP patients, 67% considered it very easy to follow compared to 19% of RO patients (<0.0001). A total of 72% of RP patients confirmed the treatment never interfered with their daily lives vs 40% of the RO group (P=0.0085). Overall satisfaction comparisons revealed that in RP patients, 60% were very satisfied vs 14% in RO patients (P<0.0001). MMSE did not demonstrate significant differences among treatment groups when compared at one and three month visits.
Winblad et al.[76] (2007) Rivastigmine patch 9.5 mg/24 hours vs rivastigmine patch 17.4 mg/24 hours vs rivastigmine 12 mg/day vs placebo	DD, PC, RCT Patients 50 to 85 years of age with MMSE scores of 10 to 20 diagnosed with Alzheimer's disease, all patients were required to be living with someone or to be in daily contact with a caregiver	N=1,195 Dose titration in 4-week intervals over 16 weeks and maintained at their highest well-tolerated dose for a further 8 weeks, total of 24 weeks	Primary: ADAS-Cog subscale (assess orientation, memory, language, visuospatial and praxis function), ADCS-CGIC (assess single global rating) Secondary: ADCS-ADL, MMSE, NPI, Ten Point Clock-drawing Test, and Trail-making Test part A	Primary: Patients in all rivastigmine groups (patch and capsule) showed significant improvements compared to placebo at week 24 with respect to ADAS-Cog and the ADCS-CGIC (all P<0.05 vs placebo). Secondary: All rivastigmine groups (patch and capsule) showed statistically significant benefits over placebo on the ADCS-ADL, MMSE and Trail-making Test part A (all P<0.05 vs placebo). Statistically significant treatment effects were not attained on the NPI or Ten Point Clock-drawing Test (P value not reported).
Winblad, Kawata et al.[77]	DB, DD, PC	N=1,059	Primary: ADCPQ	Primary: At 8 weeks, general preference was seen for the patch:

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(2007) 10 cm^2 rivastigmine patch (9.5 mg/24 hours) vs 20 cm^2 rivastigmine patch (17.4 mg/24 hours) vs rivastigmine 6 mg capsules twice daily vs placebo	ACs included different size rivastigmine patches and rivastigmine capsules	24 week	Secondary: Not reported	68% of caregivers preferred the patch over capsule form (P<0.0001). 70% of caregivers preferred the patch due to ease of schedule (P<0.0001). 55% of caregivers preferred the patch due to ease of use (P=0.0008). At 24 weeks, general preference was seen for the patch: 72% of caregivers preferred the patch over capsule form (P<0.0001). 74% of caregivers preferred the patch due to ease of schedule (P<0.0001). 64% of caregivers preferred the patch due to ease of use (P<0.0001). Caregivers preferred the patch over capsule dosage form, regardless of size of patch (P<0.0001). At 8 weeks, caregivers indicated greater satisfaction overall (P<0.0001), greater satisfaction with administration (P<0.0001), less interference with daily life with the patch than the capsule (P<0.01). Secondary: Not reported
Winblad et al.[78] (2007) Rivastigmine patch 9.5 mg/24 hours vs rivastigmine patch 17.4 mg/24 hours vs rivastigmine 12 mg/day	DB, DD, MC, PG Women or men 50 to 85 years of age with a diagnosis of dementia of the Alzheimer's type according to the DSM-IV, and probable Alzheimer's disease	N=1,195 24 weeks	Primary: ADAS-Cog, ADCS-CGIC Secondary: ADCS-ADL scale; NPI for behavior and psychiatric symptoms; MMSE for cognition; Ten Point Clock-drawing Test for assessment of visuospatial and executive functions; Trail Making Test	Primary: Patients receiving rivastigmine patches or capsules showed significant benefits compared to placebo at week 24 on the ADAS-Cog subscale (P<0.05 vs placebo for all rivastigmine groups). Treatment differences on the ADCS-CGIC were statistically significant for the 10 cm^2 patch and capsule group (all P<0.05 vs placebo). The 20 cm^2 patch did not achieve statistical significance compared to placebo in the analysis (P=0.054). Secondary: Rivastigmine patches and capsule provided statistically significant benefits over placebo on the ADCS-ADL, MMSE and Trail-making Test A (all P<0.05 vs placebo). Changes from baseline on the NPI, NPI-distress subscale, and Ten-point

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo			Part A for assessment of attention, visual tracking and motor processing speed	Clock-drawing Test in the rivastigmine groups were not significantly different from those in the placebo groups (all P>0.05).
Blesa et al.[79] (2007) Rivastigmine patch 9.5 mg/24 hours vs rivastigmine patch 17.4 mg/24 hours vs rivastigmine 12 mg/day vs placebo	DB, DD, PC ACs included different size rivastigmine patches and rivastigmine capsules, caregiver preference based on data generated during the IDEAL trial (Winblad et al)	N=1,059 24 week	Primary: ADCPQ Secondary: Not reported	Primary: At 8 weeks, general preference was seen for the patch: 68% of caregivers preferred the patch over capsule form (P<0.0001). 70% of caregivers preferred the patch due to ease of schedule (P<0.0001). 55% of caregivers preferred the patch due to ease of use (P=0.0008). At 24 weeks, general preference was seen for the patch: 72% of caregivers preferred the patch over capsule form (P<0.0001). 74% of caregivers preferred the patch due to ease of schedule (P<0.0001). 64% of caregivers preferred the patch due to ease of use (P<0.0001). Caregivers preferred the patch over capsule dosage form, regardless of size of patch (P<0.0001). At eight weeks, caregivers indicated greater satisfaction overall (P<0.0001), greater satisfaction with administration (P<0.0001), less interference with daily life with the patch than the capsule (P<0.01). Secondary: Not reported
Farlow et al.[80] (2011) Rivastigmine patch 9.5 mg/24 hours vs rivastigmine patch 17.4 mg/24 hours vs	RETRO Patients with mild-to-severe Alzheimer's disease	N=1,050 24 weeks	Primary: ADAS-cog, ADCS-CGIC, and ADCS-ADL Secondary: Not reported	Primary: In patients with moderate disease, there was a significant improvement on ADAS-cog scores with the rivastigmine 17.4 mg/24 hour patch (P=0.0009) and rivastigmine capsule (P=0.0128). For patients with moderately severe disease, there was a significant improvement in ADAS-cog scores with the rivastigmine 17.4 mg/24 hour patch (P=0.006), rivastigmine 9.5 mg/24 hour patch (P=0.0163), and rivastigmine capsule (P=0.0071) compared to placebo. For patients with severe disease, there was a significant improvement on ADCS-CGIC scores with the rivastigmine 9.5 mg/24 hour patch (P=0.037) and rivastigmine capsule (P=0.0073) compared to placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
rivastigmine 12 mg/day vs placebo				For patients with moderately severe disease, there was a significant improvement on ADCS-CGIC scores with the rivastigmine 17.4 mg/24 hour patch (P=0.043) and rivastigmine 9.5 mg/24 hour patch (P=0.0116) compared to placebo. Significant improvement on ADCS-CGIC scores were seen with the rivastigmine 17.4 mg/24 hour patch in patients with moderate disease (P=0.03) and mild to moderate disease (P=0.0455) compared to placebo. For patients with moderately severe disease, there was a significant improvement on ADCS-ADL scores with the rivastigmine 17.4 mg/24 hour patch (P=0.0211) compared to placebo. For patients with moderate disease, there was a significant improvement on ADCS-ADL scores with the rivastigmine 17.4 mg/24 hour patch (P=0.0194) and rivastigmine capsule (P=0.0077) compared to placebo. There was no significant difference in ADCS-ADL scores among the treatment groups in patients with severe AD.
Choi et al.[81] (2011) Rivastigmine patch 4.6 mg/24 hours for 4 weeks, then rivastigmine patch 9.5 mg/24 hours for 4 weeks, then rivastigmine patch 9.5 mg/24 hours and memantine 5 mg/day titrated to 20 mg/day vs	MC, OL, RCT Patients with mild-to-moderate Alzheimer's disease	N=172 24 weeks	Primary: Tolerability Secondary: Efficacy as measured by CMAI-K, ADAS-cog, K-MMSE, FAB, CGA-NPI, ADCS-ADL and CDR-SB scores	Primary: The incidence of adverse events (53.4 vs 50.6%) and discontinuation due to adverse events (6.8 vs 4.8%) was not different between patients with and without memantine, respectively. The most common adverse events were skin irritation in both treatment groups (42 vs 34.9%; P=0.71), but discontinuation was rare (4.5 vs 2.4%; P=0.74). Secondary: CMAI-K scores favored rivastigmine monotherapy vs combination therapy at the end of treatment (P=0.01). Changes in other efficacy measures (ADAS-cog, K-MMSE, FAB, CGA-NPI, ADCS-ADL and CDR-SB) were not significantly different.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
rivastigmine patch 9.5 mg/24 hours				
Farlow et al.[82] (2010) Rivastigmine patch 9.5 mg/24 hours and memantine vs rivastigmine patch 9.5 mg/24 hours	OL, RCT Patients ≥50 years of age with mild-to-moderate Alzheimer's disease who had been receiving donepezil for at least 6 months and at a stable dose of 5-10 mg/day for a minimum of 3 months	N=261 25 weeks	Primary: Safety and tolerability of rivastigmine transdermal patch, with or without concomitant memantine Secondary: Changes in cognition, global functioning and activities of daily living measured by MMSE and ADCS-ADL using the CGIC	Primary: The incidences of adverse events (73.3 vs 67.5%) and serious adverse events (10.4 vs 7.1%) were both slightly higher in patients receiving concomitant memantine, but the differences were NS (95% CIs, -5.2 to 16.9 and -3.6 to 10.1 for adverse events and serious adverse events, respectively). The most frequent adverse events in the combination therapy group and the rivastigmine monotherapy group were application site reactions (17.5 vs 13.5%, respectively) and agitation (5.9 vs 7.9%, respectively). Secondary: Concomitant memantine was associated with no significant changes in efficacy, as assessed by CGIC and MMSE scores. Global functioning remained unchanged or improved (CGIC rating ≤4) in 57.7 and 67.2% of patients with memantine and patients without memantine, respectively (P=0.604). ADCS-ADL scores deteriorated from baseline in both groups, with significant worsening in patients receiving memantine compared to those not receiving memantine (mean change from baseline rivastigmine and memantine vs rivastigmine monotherapy: -5.3 vs -2.0; P=0.043).
Harry et al.[83] (2005) Donepezil with doses ranging from 5 to 10 mg/day or galantamine with doses ranging from 8 to 36 mg/day	MA Patients with mild-to-moderate Alzheimer's disease, and without diagnosis of any other psychiatric or neurological disorder	N=3,353 3 donepezil studies 5 galantamine studies Duration varied	Primary: ADAS-Cog or MMSE Secondary: Not reported	Primary: The majority of patients showed no difference compared to placebo. There was no significant difference in efficacy between the groups. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				
Wilcock et al.[84] (2003) Donepezil 10 mg/day vs galantamine 24 mg/day	MC, PG, RCT Patients with Alzheimer's disease	N=182 52 weeks	Primary: BrADL Secondary: MMSE, ADAS-Cog, NPI	Primary: BrADL total score showed no significant difference between treatment groups in mean change from baseline to week 52. Secondary: Galantamine patients' scores on the MMSE at week 52 did not differ significantly from baseline, whereas donepezil patients' scores deteriorated significantly from baseline (P<0.0005).The between group difference in MMSE change did not reach statistical significance. In the ADAS-Cog analysis, between group differences for the total population were NS, whereas galantamine treated patients with MMSE scores of 12 to 18 demonstrated an increase (worsening) in the ADAS-Cog score of 1.61+/-0.80 vs baseline, compared to an increase of 4.08+/-0.84 for patients treated with donepezil. More caregivers of patients receiving galantamine reported reductions in burden compared to donepezil. Changes from baseline in NPI were similar for both treatments.
Jones et al.[85] (2004) Donepezil 10 mg/day vs galantamine 12 mg twice daily	OL, RCT Patients with Alzheimer's disease	N=120 12 weeks	Primary: Ease of use and tolerability, ADAS-Cog, effects on cognition and activities of daily living Secondary: Not reported	Primary: Physicians and caregivers reported statistically significant greater satisfaction/ ease of use with donepezil compared to galantamine at weeks four and 12. Significantly greater improvements in cognition were observed for donepezil vs galantamine on the ADAS-Cog at week 12 and at endpoint. Activities of daily living improved significantly in the donepezil group compared to the galantamine group at weeks four and 12 (P<0.05). Forty-six percent of galantamine patients reported gastrointestinal adverse events vs 25% of donepezil patients.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Modrego et al.[86] (2010) Donepezil 10 mg/day vs memantine 20 mg/day	PG, RCT, SB Patients with mild-to-moderate Alzheimer's disease	N=63 6 months	Primary: ADAS-cog, NPI, DAD, changes in N-acetylaspartate metabolite levels Secondary: Not reported	Primary: There were no significant differences in the clinical scales with donepezil and memantine (donepezil: ADAS-cog, -0.12; P=NS, NPI, -0.04; P=NS, DAD, 6.67; P=0.014) (memantine: ADAS-cog, -1.37; P=NS, NPI, 1.25; P=NS, DAD, 4.46; P=NS). More patients worsened than improved on either drug. Daily living activities decreased by 4.4% in the memantine group and 6.6% in the donepezil group (P=0.6). At baseline, N-acetylaspartate/Cr ratio in the PCG correlated significantly with the ADAS-cog (P=0.02) and MEC (P=0.02). The N-acetylaspartate/Cr ratio correlated with the baseline ADAS-cog (P=0.02) in the left temporal lobe. At week 24, the PCG was the only area where the correlation was significant. The patients who improved in the ADAS-cog showed increases in the N-acetylaspartate/Cr ratios (P=0.004). None of the baseline metabolite levels predicted response to treatment in any of the examined areas. Secondary: Not reported
Rozankovic et al.[87] (2021) [Abstract only] Donepezil vs Memantine	OL, RCT Patients with moderate Alzheimer's disease	N=85 6 months	Primary: NPI at baseline to six months Secondary: Not reported	Primary: The NPI total score improved from baseline to month six in both groups (P<0.0001). Analyses of the NPI subdomains revealed that both donepezil treatment and memantine treatment produced statistically significant improvement in all of the NPI domains except euphoria and apathy, for which no improvement was observed after memantine treatment. Secondary: Not reported
Wilkinson et al.[88]	OL, RCT	N=111	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2002) Donepezil 10 mg/day vs rivastigmine 6 mg twice daily	Patients with mild-to-moderate Alzheimer's disease	12 weeks	ADAS-Cog, tolerability Secondary: Not reported	More patients taking donepezil completed the study (89.3%) compared to the rivastigmine group (69.1%; P=0.009). 10.7% of the donepezil group and 21.8% of the rivastigmine group discontinued treatment due to adverse events. 87.5% of the donepezil patients and 47.3% of the rivastigmine patients remained on the maximum approved dose of each drug at the last study visit. Both groups showed comparable improvements in ADAS-Cog administered at weeks four and 12. Secondary: Not reported
Van Puyvelde et al.[89] (2011) Galantamine vs donepezil or rivastigmine (safety control group)	MC, OS, PRO Patients with mild-to-moderate Alzheimer's disease	N=128 6 months	Primary: Safety, patients and caregiver satisfaction, global impression as reported by the physician Secondary; Not reported	Primary: Adverse events were similar among both treatment groups (galantamine, 34%; SCG, 34.4%). The incidence of serious (12 events) and severe (15 events) adverse events with galantamine was similar to the SCG group (serious: galantamine 9.3% vs safety control group 9.7%); severe: galantamine 11.3% vs safety control group 12.9%. A total of 84.5% of patients treated with galantamine continued their treatment after six months. Patients receiving galantamine reported their condition as improved (49%), unchanged (47%) and worsened (4%). Caregivers rated global evaluation as better (37%), unchanged (41%) and worse (22%) with galantamine. Physicians rated global clinical impression of change as better (46%), unchanged (34%) and worse (20%) with galantamine. Measurements of cognition and behavior remained stable. The appreciation of physicians and caregivers corresponded well (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Tariot et al.[90] (2004) Memantine 20 mg/day vs donepezil	DB, MC, PC, RCT Patients with moderate-to-severe Alzheimer's disease who received stable doses of donepezil	N=404 24 weeks	Primary: SIB, ADCS-ADL, CIBIC-Plus, BGP Secondary: Not reported	Primary: A significantly greater therapeutic effect was observed in the memantine group than in the placebo group on the ADCS-ADL, SIB and CIBIC-Plus. Patients receiving memantine in combination with donepezil demonstrated significantly less decline in ADCS-ADL scores compared to patients receiving donepezil-placebo over the 24-week study period (P=0.02). Patients receiving memantine showed significantly less cognitive decline in SIB scores compared to patients receiving placebo. Therapy with memantine-donepezil resulted in sustained cognitive performance above baseline compared to the progressive decline seen with the donepezil-placebo treatment. The change in total mean scores favored memantine vs placebo for the CIBIC-Plus (possible score range was 1-7), 4.41 vs 4.66, respectively (P=0.03). Treatment discontinuations due to adverse events for memantine vs placebo were 7.4% of the patients compared to 12.4%. Secondary: Not reported
Bullock et al.[91] (2005) Rivastigmine 3 to 12 mg/day vs donepezil 5 to 10 mg/day	DB, MC, RCT Patients 50 to 85 years of age with moderate to moderately-severe Alzheimer's disease (MMSE score 10-20)	N=994 24 months	Primary: SIB Secondary: GDS, ADCS-ADL, MMSE, NPI	Primary: Donepezil-treated patients declined 9.91 points from baseline on the SIB as compared to rivastigmine-treated patients, who declined by 9.30 points (P=NS). Secondary: Rivastigmine was more effective than donepezil on the ADCS–ADL, on which there was a between-treatment difference of 2.1 points after two years (P=0.007), and greater efficacy on the GDS (P=0.049). There were no significant differences in MMSE and NPI between the treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				More patients receiving rivastigmine reported 'any adverse event' compared to those receiving donepezil during the titration phase (82.0 and 64.7%, respectively). Adverse events were higher with rivastigmine during the titration phase and included nausea (32.9 vs 15.2%) and vomiting (27.9 vs 5.8%). In the maintenance phase, adverse event rates in the two groups were similar (78.7% for the rivastigmine group and 76.9% for the donepezil group). Premature discontinuations due to adverse events were higher in the rivastigmine group during the titration phase (14.1 vs 7.0% for donepezil) but similar in the maintenance phase (17.9 vs 14.1% for donepezil).
Mossello et al.[92] (2004) Donepezil 5 to 10 mg/day vs galantamine 16 to 24 mg/day vs rivastigmine 6 to 12 mg/day	OL, OS Patients with mild-to-moderate Alzheimer's disease	N=407 9 months	Primary: MMSE, ADL and IADL Secondary: Not reported	Primary: There were no differences amongst the three groups in regard to any of the outcome measures (galantamine was not included in the MMSE comparison due to the small number of treated patients). Discontinuation due to adverse effects was lower in those patients on donepezil (3%) vs rivastigmine (17%; P=0.01) and vs galantamine (21%; P=0.01). Secondary: Not reported
Aguglia et al.[93] (2004) Donepezil vs galantamine vs rivastigmine	OL Patients with Alzheimer's disease	N=242 6 months	Primary: MMSE, ADAS-Cog, ADL and IADL Secondary: Not reported	Primary: There were no statistical differences on changes in the MMSE, ADAS-Cog, ADL or IADL measures amongst the three groups. There were no differences on changes in the IADL measure among the three groups. In the ADL measure, donepezil and galantamine patients showed a decrease while there was no change for rivastigmine patients. Rivastigmine showed a small numerical advantage (but not statistically) compared to donepezil and galantamine on the ADAS-Cog.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Lopez-Pousa et al.[94] (2005) Donepezil vs galantamine vs rivastigmine vs historical controls	OL, PRO Patients with mild-to-moderate Alzheimer's disease	N=147 6 months	Primary: MMSE Secondary: Not reported	Primary: All three treatment groups had better MMSE scores compared to control (donepezil; P<0.001, galantamine; P<0.01, and rivastigmine; P<0.03). There were no statistical differences between the groups on measures of cognitive decline (via MMSE). Secondary: Not reported
Rodda et al.[95] (2009) Donepezil 5 to 10 mg/day vs galantamine 8 to 24 mg/day vs rivastigmine 9 to 17.4 mg/day	RETRO Patients with Alzheimer's disease being treated with donepezil, rivastigmine or galantamine monotherapy	N=6,110 12 to 170 weeks	Primary: NPI Secondary: Not reported	Primary: Three of the 14 studies reviewed reported statistically significant improvement in overall NPI score or in the agitation/aggression item of the NPI only. One study demonstrated a significant difference in NPI score between groups randomized to either continuation or discontinuation of donepezil (placebo following an initial OL treatment phase. Of these four positive studies, two specified a minimum level of behavioral disturbance at baseline and used behavioral scores as a primary outcome. Secondary: Not reported
Howard et al.[96] (2012)	DB, MC, RCT	N=295	Primary: Standardized Mini-	Primary: Mean donepezil vs placebo Standardized Mini-Mental State Examination

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Donepezil 10 mg/day vs memantine 20 mg/day vs donepezil 10 mg/day and memantine 20 mg/day vs placebo	Community-based patients with moderate-to-severe Alzheimer's disease who were taking donepezil 10 mg/day for ≥3 months	52 weeks	Mental State Examination and BADLS scores Secondary: NPI, caregiver health status assessed by General Health Questionnaire 12	scores were higher with donepezil (better cognitive function) by an average of 1.9 points (95% CI, 1.3 to 2.5; P<0.001) and BADLS scores were lower (less functional impairment) by 3.0 points (95% CI, 1.3 to 2.5; P<0.001). Both outcomes demonstrated significant heterogeneity in treatment efficacy over tome (P=0.002 and P=0.004, respectively), with less benefit apparent at the six week assessment than at later time points. From six weeks onward, differences were roughly parallel. Mean donepezil+memantine vs placebo+memantine Standardized Mini-Mental State Examination scores were higher with donepezil by an average of 1.2 points (95% CI, 0.6 to 1.8; P<0.001) and BADLS scores were lower by 1.8 points (95% CI, 0.3 to 2.8; P<0.001). Both outcomes were smaller than the minimum clinically important difference. Interactions of memantine therapy with visit were NS. Both donepezil and memantine demonstrated benefits on both Standardized Mini-Mental State Examination and BADLS larger in the absence of other agents alone, though statistically insignificant (P=0.14 and P=0.09, respectively). No significant benefits were seen adding memantine to donepezil on Standardized Mini-Mental State Examination scores (0.8 points higher with memantine and placebo; 95% CI, -0.1 to 1.6; P=0.07) or BADLS scores (0.5 points lower with memantine than placebo; 95% CI, 2.2 to 1.2; P=0.57). Secondary: NPI scores were lower for patients on memantine compared to placebo, indicating fewer behavioral and psychological symptoms by 4.0 points (99% CI, 0.6 to 7.4; P=0.002). No observable NPI differences noted with continuation, as compared to discontinuation of donepezil therapy (2.3 points lower with continuation; 95% CI, -1.1 to 5.7; P=0.08). Donepezil+memantine vs donepezil demonstrated a lower NPI score by 5.1 points (99% CI, 0.3 to 9.8; P=0.006). Continuation of donepezil and donepezil+memantine compared to the placebo and memantine + placebo demonstrated larger average decreases

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(indicating fewer psychological symptoms) across trial visits in General Health Questionnaire 12 scores for caregiver health status. There was a 0.5 point larger decrease with continuation vs discontinuation of donepezil (99% CI, -0.01 to 1.0; P=0.01) and 0.5 point larger decrease with memantine vs placebo (95% CI, -0.1 to 0.9; P=0.03), though significance was not reached to allow for multiple secondary outcomes.
Porsteinsson et al.[97] (2008) Memantine 20 mg/day plus cholinesterase inhibitor vs cholinesterase inhibitor plus placebo	PC, R Patients with probable Alzheimer's disease, MMSE scores between 10 to 22, concurrently taking a cholinesterase inhibitor	N=433 24 weeks	Primary: ADAS-cog, CIBIC-Plus Secondary: ADCS-ADL, NPI, MMSE	Primary: No significant difference in ADAS-cog and CIBIC-Plus was found between memantine and placebo. Secondary: No significant difference in ADCS-ADL, NPI or MMSE was found between memantine and placebo.
Cumming et al.[98] (2006) Memantine 20 mg/day plus donepezil vs donepezil	DB, PC, PG, PRO Patients with moderate-to-severe Alzheimer's disease who received stable doses of donepezil	N=404 24 weeks	Primary: NPI Secondary: Not reported	Primary: NPI scores significantly favored the memantine group at 12 weeks and at 24 weeks. At week 12, NPI scores increased (worsening behavior) 1.7 points in the placebo group and decreased 2.5 points in the memantine group (P<0.001). At week 24, NPI scores increased 3.7 points (worsening behavior) in the placebo groups and the memantine group returned to baseline (P=0.002). Fewer patients developed delusions in the memantine treatment group than the placebo group (P=0.011). Secondary: Not reported
Maidment et al.[99] Memantine 20 mg daily	MA Patients with probable	N=1,750 Duration varied	Primary: NPI Secondary:	Primary: Compared to the placebo group patients receiving memantine improved by 1.99 on the NPI scale (95% CI, -0.08 to -3.91; P=0.041).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo or memantine 20 mg daily in combination with a cholinesterase inhibitor (doses varied) vs placebo in combination with a cholinesterase inhibitor (doses varied)	Alzheimer's disease		Not reported	Secondary: Not reported
Wilkinson et al.[100] (2009) Cholinesterase inhibitors (donepezil 5 or 10 mg/day) vs placebo	MA Patients with mild-to-moderate Alzheimer's disease	N=906 (3 trials) 24 weeks	Primary: MMSE Secondary: Not reported	Primary: A significantly greater percentage of placebo patients than donepezil-treated patients met the specified criteria for all three definitions of clinical worsening. The OR for clinical worsening were significantly reduced for donepezil-treated patients compared to placebo patients (P<0.0001 for all definitions). Among patients meeting criteria for clinical worsening, mean declines in MMSE scores were greater for placebo than donepezil-treated patients. This outcome was also apparent when milder (MMSE, 18 to 26) and more moderate (MMSE, 10 to 17) subgroups were analyzed separately. Secondary: Not reported
Feldman et al.[101]	OS, PRO	N=548	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2009) Cholinesterase inhibitors	Alzheimer's disease patients with and without cerebrovascular disease	7 years	Time to nursing home placement Secondary: Identify factors noted to reduce risk of NHP, including measurement of DAD and MMSE	The overall median time to permanent institutional admission was 42.4 months (95% CI, 38.0 to 48.0 months). Secondary: Factors noted to reduce the risk of being admitted to a nursing home included higher baseline DAD and MMSE scores, Alzheimer's disease diagnosis, living with caregiver, country, and treatment duration (P<0.05). Each year of treatment demonstrated a reduced risk of nursing home admission (galantamine, -31%, other cholinesterase inhibitors, -29%).
Trinh et al.[102] (2003) Cholinesterase inhibitors vs placebo	MA Trials included outpatients with mild or moderate Alzheimer's disease who were treated for at least one month with a cholinesterase inhibitor	29 trials Duration varied	Primary: NPI, ADAS-noncog, ADL and IADL Secondary: Not reported	Primary: Cholinesterase inhibitors improved the NPI statistically better than placebo (95% CI, 0.87 to 2.57). Cholinesterase inhibitors improved the ADAS-noncog measure numerically but not statistically compared to placebo (95% CI, 0.0 to 0.05). Cholinesterase inhibitors improved ADL numerically but not significantly better than placebo (95% CI, 0.0 to 0.19). Cholinesterase inhibitors improved IADL statistically compared to placebo (95% CI, 0.01 to 0.17). Secondary: Not reported
Lanctot et al.[103] (2003) Cholinesterase inhibitors vs placebo	MA Adult patients diagnosed with Alzheimer's disease	N=7,954 16 trials that varied in duration	Primary: Global responders, using CGI-C, CIBIC, adverse, events, dropouts Secondary: Not reported	Primary: For cholinesterase inhibitors the pooled mean proportion of global responders was in excess by 9% when compared to the placebo treatment (9%; 95% CI, 6 to 12). In the cholinesterase inhibitor treatment groups the rates of adverse events, dropout for any reason and dropout because of adverse events were higher compared to the placebo treatment groups (8%; 95% CI, 5 to 11; 8%; 95% CI, 5 to 11; and 7%; 95% CI, 3 to 10). The number needed to treat for one additional patient to benefit was 7

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(95% CI, 6 to 9) for stabilization or better, 12 (95% CI, 9 to 16) for minimal improvement or better and 42 (95% CI, 26 to 114) for marked improvement. The number needed to treat for one additional patient to experience an adverse event was 12 (95% CI, 10 to 18). Secondary: Not reported
Birks et al.[104] (2006) Cholinesterase inhibitors vs placebo	MA Patients diagnosed with mild, moderate or severe dementia due to Alzheimer's disease	N=7,298 Minimum 6 months	Primary: CIBIC-Plus, GBS, GDS, ADAS-Cog, MMSE, SIB, NPI, ADL scored by PDS and DAD Secondary: Withdrawals prior to six months, adverse events	*Cholinesterase inhibitor vs placebo (12 trials)* Primary: Significant benefit was seen in CIBIC-Plus for patients treated with a cholinesterase inhibitor over placebo; more patients were scored as "showed improvement" than "showed decline/no change" (OR, 1.56; 95% CI, 1.32 to 1.85; P<0.00001): eight studies. No significant difference was seen in GBS between the cholinesterase inhibitor and placebo groups at one year (P value not reported): one trial. Significant improvement in ADAS-Cog was found for patients treated with donepezil, galantamine, or rivastigmine over placebo (WMD, –2.66; 95% CI, –3.02 to –2.31; P<0.00001): 10 studies. Significant benefit was seen in MMSE for patients treated with a cholinesterase inhibitor over placebo (WMD, 1.37; 95% CI, 1.13 to 1.61; P<0.00001): nine studies. Significant benefit was seen in ADL-PDS and DAD for patients treated with a cholinesterase inhibitor over placebo (WMD, 2.40; 95% CI, 1.55 to 3.37; P<0.00001 for PDS; and WMD, 4.39; 95% CI, 1.96 to 6.81; P=0.0004 for DAD). Significant benefit was seen in NPI for patients treated with a cholinesterase inhibitor over placebo (WMD, –2.44; 95% CI, –4.12 to –0.76; P=0.004). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Significantly more patients treated with a cholinesterase inhibitor (29%) withdrew prior to six months than those in the placebo groups (18%; P<0.00001). Adverse events that occurred significantly more frequently in the cholinesterase inhibitor group than the placebo group, from pooled data from at least 6 trials included: abdominal pain, anorexia, dizziness, diarrhea, headache (P<0.0001), insomnia (P=0.007), nausea, vomiting (P<0.00001 unless noted). *Donepezil vs rivastigmine (one trial)* Primary: There was no statistically significant difference between the treatment groups for cognitive function, ADL scales, behavior disturbances and global assessment (P values not reported). Secondary: Significantly fewer patients in the donepezil group withdrew from treatment after 2 years than in the rivastigmine group (OR, 0.64; 95% CI, 0.50 to 0.83; P=0.0006). Adverse events that occurred significantly more frequently at 12-16 weeks of treatment in the rivastigmine group than in the donepezil group included: nausea (P<0.00001), vomiting (P<0.00001), falls (P=0.01), hypertension (P=0.01), anorexia (P=0.0005) and weight loss (P=0.001), and after 16 weeks to 2 years of treatment: nausea (P=0.0002), vomiting (P<0.00001) and anorexia (P=0.02). No significant difference between treatment groups for serious adverse events was noted (P value not reported).
Hansen et al.[105] (2008) Cholinesterase inhibitors	MA Patients with Alzheimer's disease	26 trials Variable duration	Primary: Cognition (ADAS-cog), function, behavior (NPI), global assessment of change (CIBIC+ and CGI-C)	Primary: <u>Cognition (14 studies)</u> The pooled WMD in change between active treatment and placebo was -2.67 (95% CI -3.28 to -2.06) for donepezil, -2.76 (95% CI -3.17 to -2.34) for galantamine, and -3.01 (95% CI -3.80 to -2.21) for rivastigmine. <u>Function (14 studies)</u>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Not reported	The pooled standardized mean difference between active treatment and placebo was 0.31 (95% CI, 0.21 to 0.40) for donepezil, 0.27 (95% CI, 0.18 to 0.36) for galantamine, and 0.26 (95% CI, 0.11 to 0.40) for rivastigmine. Behavior (seven studies) The pooled WMD in NPI score between active treatment and placebo was -4.3 (95% CI, -5.95 to -2.65) for donepezil and -1.44 (95% CI, -2.39 to -0.48) for galantamine. Global assessment of change (nine studies) The pooled RR of responding for active treatment compared to placebo was 1.88 (95% CI, 1.50 to 2.34) for donepezil, 1.15 (95% CI, 0.96 to 1.39) for galantamine, and 1.64 (95% CI, 1.29 to 2.09) for rivastigmine. Secondary: Not reported
Kim et al.[106] (2011) Cholinesterase inhibitors	MA Cognitively impaired older adults	54 trials Variable duration	Primary: Falls, syncope, fracture and accidental injury reported Secondary: Not reported	Primary: Cholinesterase inhibitors usage was associated with the greatest risk of syncope compared to placebo (OR, 1.53; 95% CI, 1.02 to 2.30), but not with any other events: falls (OR, 0.88; 95% CI, 0.74 to 1.04); fracture (OR, 1.39; 95% CI, 0.75 to 2.56); accidental injury (OR, 1.13; 95% CI, 0.87 to 1.45). Memantine was associated with fewer fractures (OR, 0.21; 95% CI, 0.05 to 0.85), but not with other events: falls (OR, 0.92; 95% CI, 0.72 to 1.18), syncope (OR, 1.04; 95% CI, 0.35 to 3.04); accidental injury (OR, 0.80; 95% CI, 0.56 to 1.12). There were no differential effects noted according to type and severity of cognitive impairment, residential status, or length of follow-up.
Alzheimer's Disease				
Haeberlein SB et al.[107] (2022) EMERGE & ENGAGE	Two DB, MC, PC, RCT Patients 50 to 85 years of age who met clinical criteria	N=1,638 (EMERGE) and 1,647 (ENGAGE) 78 weeks	Primary: Change from baseline to week 78 on CDR-SB Secondary:	Primary: *Note: An independent data monitoring committee reviewed the unblinded results of the interim analysis and made the recommendation to the sponsor to terminate the studies, which occurred on March 21, 2019. Following this futility announcement (March 21, 2019), all dosing stopped at the study sites, and data collection and data cleaning continued. The*

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Aducanumab low-dose (titrated to target dose of 3 mg/kg for ApoE ε4+ or 6 mg/kg for for ApoE ε4-) IV every four weeks vs aducanumab high-dose (titrated to a target dose of 6 mg/kg for ApoE ε4+ or 10 mg/kg for for ApoE ε4-) IV every four weeks vs placebo	for MCI due to Alzheimer's disease or mild Alzheimer's disease dementia, with amyloid pathology confirmed by visual assessment of amyloid PET, MMSE score of 24 to 30, and CDR global score of 0.5.		MMSE, ADAS-Cog13, ADCS-ADL-MCI, biomarker endpoints and safety assessments	*prespecified futility methodology used pooled data from EMERGE and ENGAGE to predict the future unobserved treatment effect. The individual study results using the prespecified primary efficacy analysis methods on the futility data set showed a -18% treatment difference on the CDR-SB, favoring high-dose aducanumab in EMERGE, and a 15% treatment difference on CDR-SB, favoring placebo in ENGAGE. This refuted an assumption of conditional power (i.e., that the treatment effect in the two studies would be similar), so conditional power was then recalculated using the data from each of the two studies to predict the future unobserved treatment effect, and this non-pooled analysis yielded estimates of 59% and 0% on the primary endpoint for the high-dose groups in EMERGE and ENGAGE, respectively.* High-dose aducanumab in EMERGE demonstrated a difference of -0.39 vs placebo in the mean change from baseline in CDR-SB score at week 78 (95% CI, -0.69 to -0.09; P=0.012), a 22% reduction in decline. Results from the low-dose aducanumab arm were not statistically significant compared to placebo on the primary endpoint. In ENGAGE, the difference in mean change from baseline in CDR-SB scores at week 78 was 0.03 with high-dose aducanumab vs placebo (95% CI, -0.26 to 0.33; P=0.833), an increase of 2%. Results from the low-dose aducanumab arm were not statistically significant compared to placebo on the primary endpoint. Secondary: In EMERGE, the high-dose aducanumab arm also showed less decline vs placebo on each of the three specified secondary endpoints: MMSE (difference of 0.6 vs placebo in mean change from baseline; -18%; P=0.049), ADAS-Cog13 (difference of -1.40 vs placebo in mean change from baseline; -27%; P=0.010), and ADCS-ADL-MCI (difference of 1.7 vs placebo in mean change from baseline; -40%; P<0.001) at week 78. Results from three out of four endpoints from the low-dose aducanumab arm were numerically intermediate between those of the high-dose and placebo arms but not statistically significant vs placebo on any secondary endpoint.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				In ENGAGE, in the high-dose aducanumab arm, the differences in mean change from baseline at week 78 vs placebo on the MMSE (-0.1; 3%; P=0.811), ADAS-Cog13 (-0.59; -11%; P=0.258), and ADCS-ADL-MCI (0.7; -18%; P=0.151) were not statistically significant. Results from the low-dose aducanumab arm were not statistically significant vs placebo on any of the secondary endpoints and were consistent with those from EMERGE. Amyloid PET substudies assessed 488 and 585 patients in EMERGE and ENGAGE, respectively. These substudies showed a dose- and time-dependent reduction in amyloid PET SUVR in both EMERGE and ENGAGE. At week 78, the difference in adjusted mean change from baseline between high-dose aducanumab and placebo was -0.278 (95% CI, -0.306 to -0.250; P<0.0001) for EMERGE and -0.232 (95% CI, -0.256 to -0.208; P<0.0001) for ENGAGE. For the high-dose aducanumab arm, the reduction in adjusted mean change from baseline in amyloid PET SUVR in ENGAGE was 16.5% less than that in EMERGE at week 78. The adjusted mean changes from baseline in amyloid PET SUVR for low-dose aducanumab arms were similar between EMERGE and ENGAGE at week 78. The incidence of adverse events was similar across dose groups in both studies. Adverse events with an incidence >10% in any dose group were ARIA-E, headache, brain microhemorrhages, nasopharyngitis, fall, localized superficial siderosis and dizziness. The incidence of ARIA-E was higher in the high-dose groups compared with low-dose groups (35% vs 26%, respectively, in EMERGE and 36% vs 26%, respectively, in ENGAGE).
van Dyck et al.[108] (2023) Clarity AD Lecanemab 10 mg/kg biweekly vs	DB, MC, RCT Patients 50 to 90 years of age with either mild cognitive impairment due to Alzheimer's disease	N=1,795 18 months	Primary: The change in score on the Clinical Dementia Rating (CDR)-Sum of Boxes (CDR-SB) from baseline at 18 months	Primary: The mean CDR-SB score at baseline was approximately 3.2 in both the lecanemab and placebo groups, findings consistent with early Alzheimer's disease (score 0.5 to 6). The adjusted mean change from baseline at 18 months in the CDR-SB score was 1.21 in the lecanemab group and 1.66 in the placebo group (difference, -0.45; 95% CI, -0.67 to -0.23; P<0.001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	or mild Alzheimer's disease-related dementia with evidence of amyloid on PET or by cerebrospinal fluid testing		Secondary: Change from baseline at 18 months in the following: amyloid burden on PET as measured in centiloids (with either florbetaben, florbetapir or flutemetamol tracers) in a substudy, the score on the 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale, the Alzheimer's Disease Composite Score, and the score on the Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment	In the substudy of amyloid burden on PET involving 698 participants, the mean amyloid level at baseline was 77.92 centiloids in the lecanemab group and 75.03 centiloids in the placebo group. The adjusted mean change from baseline at 18 months was -55.48 centiloids in the lecanemab group and 3.64 centiloids in the placebo group (difference, -59.12 centiloids; 95% CI, -62.64 to -55.60; P=0.001). Other mean differences between the two groups in the change from baseline favoring lecanemab were as follows: for the ADAS-cog14 score, -1.44 (95% CI, -2.27 to -0.61; P<0.001); for the ADCOMS, -0.050 (95% CI, -0.074 to -0.027; P<0.001); and for the ADCS-MCI-ADL score, 2.0 (95% CI, 1.2 to 2.8; P<0.001). Lecanemab resulted in infusion-related reactions in 26.4% of the participants and amyloid-related imaging abnormalities with edema or effusions in 12.6%.
Dementia of Parkinson's Disease				
Emre et al.[109] (2004) Rivastigmine 3 to 12 mg/day; average dose 8.6 mg/day	DB, MC, PC, RCT Patients at least 50 years of age with mild-to-moderate dementia developed 2 years after the	N=541 Dose titration over the first 16 weeks with a subsequent	Primary: ADAS-Cog, ADCS-CGIC Secondary: ADCS-ADL, NPI-10, MMSE, CDR	Primary: Patients who were receiving rivastigmine had significant improvement of 2.1 points in the 70-point ADAS-Cog scores vs worsening of 0.7 point in the placebo group from baseline (P<0.001). 19.8% of patients in the rivastigmine group and 14.5% in the placebo group clinically improved in the ADCS-CGIC scores. 13% of patients in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	diagnosis of Parkinson's disease	assessment period of 8 weeks Total of 24 weeks	power of attention tests, D-KEFS verbal fluency test, Ten Point Clock-drawing Test	the rivastigmine group and 23.1% in the placebo group clinically worsened in the ADCS-CGIC scores (P=0.007). Secondary: All secondary outcomes were significantly better in the rivastigmine group compared to placebo, as reflected by the changes in the ADCS-ADL score (P=0.02), NPI-10 (P=0.02), MMSE (P=0.03), CDR power of attention tests (P=0.009), D-KEFS verbal fluency test (P<0.001), and the Ten Point Clock-drawing Test (P=0.02).
Wesnes et al.[110] (2005) Rivastigmine 3 to 12 mg/day, average dose 8.6 mg/day vs placebo	DB, MC, PC, RCT Patients at least 50 years old with Parkinson's disease	N=487 24 weeks	Primary: Power of attention, continuity of attention, cognitive reaction time, reaction time variability Secondary: Not reported	Primary: At week 16, there was no statistical significance from baseline scores between rivastigmine and placebo for power of attention (P=0.11) but there was a significance at week 24 (P<0.01). By week 16, there was a significant improvement with continuity of attention (P=0.001) compared to placebo and this parameter continued to improve at week 24 (P=0.0001). Cognitive reaction time showed significant improvement by the end of week 24 (P<0.001) vs week 16 (P=0.064) but declined with placebo. Reaction time variability continued to show improvement over placebo from week 16 (P<0.05) to week 24 (P<0.001). Secondary: Not reported
Schmitt et al.[111] (2010) Rivastigmine 3 to 12 mg/day vs placebo	DB, MC, PC, RCT Patients with Parkinson's disease dementia	N=541 24 weeks	Primary: Executive function as assessed by D-KEFS measures Secondary: Not reported	Primary: Rivastigmine was associated with significantly more correct responses, fewer set loss errors, and more total responses made (within time available), compared to placebo (all P<0.05). There was no significant difference in total repetition errors (P=0.57). Rivastigmine was associated with a significantly higher Card Sorting recognition description score than placebo (P=0.03). Word reading errors, word comprehension, and sort recognition errors were NS. There were significantly more correct substitutions on the Symbol Digit Modalities Test compared to placebo (P=0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Rivastigmine was associated with significantly fewer self-corrected errors on the Color-Word Interference inhibition/switching subtest compared to placebo (P=0.049). Treatment differences in numbers of correct responses were near statistical significance (P=0.050). Other treatment differences in this battery of executive function tests were not statistically significant. Secondary: Not reported
Olin et al.[112] (2010) Rivastigmine 3 to 12 mg/day vs placebo	DB, MC, PC, RCT Patients ≥50 years of age with Parkinson's disease dementia	N=541 24 weeks	Primary: Tolerability and efficacy as measured by ADCS-ADL Secondary: Not reported	Primary: A total of 75.8% of patients completed the study (rivastigmine, 72.7% vs placebo, 82.1%). The primary reasons for discontinuation were adverse events (17.1% for rivastigmine vs 7.8% for placebo) and withdrawal of consent (5.8% rivastigmine vs 1.1% placebo). At 24 weeks, rivastigmine was associated with significantly less deterioration compared to placebo based on ADCS-ADL total scores (-1.1 vs -3.6, respectively; P=0.023). Similar improvements were seen with rivastigmine compared to placebo on the basic ADCS-ADL subscale (-0.5 vs -1.7, respectively; P=0.025), and on high level function ADLs (0.1 vs -1.0; P=0.017). No other measures were significantly different among the treatment groups. Secondary: Not reported
Maidment et al.[113] (2006) Rivastigmine 3 to 12 mg/day vs placebo	MA Patients diagnosed with mild-to-moderately severe dementia, which developed at least 2 years after Parkinson's disease was diagnosed	N=541 (1 study) 24 weeks	Primary: ADAS-Cog, ADCS-CGIC Secondary: MMSE, ADCS-ADL, NPI, CDR, D-KEFS, Ten Point Clock-drawing Test, UPDRS, adverse events	Primary: Significant improvement in ADAS-Cog was found for patients treated with rivastigmine over placebo (WMD, –2.80; 95% CI, –4.26 to –1.34; P=0.0002). Results in ADCS-CGIC significantly favored patients treated with rivastigmine over placebo (WMD, –0.50; 95% CI, –0.77 to –0.23; P=0.0004). 19.8% of rivastigmine patients experienced "clinically meaningful (moderate or marked) improvement" compared to 14.5% of the placebo group; 13.0% of rivastigmine patients experienced "clinically meaningful worsening" compared to 23.1% in the placebo group (P values not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Results for MMSE significantly favored patients treated with rivastigmine over placebo (WMD, 1.00; 95% CI, 0.33 to 1.67; P=0.003). Results for ADCS-ADL significantly favored patients treated with rivastigmine over placebo (WMD, 2.50; 95% CI, 0.43 to 4.57; P=0.02). Results for NPI significantly favored patients treated with rivastigmine over placebo (WMD, –2.00; 95% CI, –3.91 to –0.09; P=0.04). For CDR no statistically significant difference was found (P=0.25). For D-KEFS, results significantly favored patients treated with rivastigmine over placebo (WMD, 2.80; 95% CI, 1.47 to 4.13; P<0.0001). Full UPDRS was not reported. No statistically significant difference was found for motor score, including tremor (P=0.83 and P=0.84). Significantly more patients in the rivastigmine group than the placebo group experienced one or more adverse events (P=0.0006). Adverse events included: nausea, vomiting, tremor, and dizziness. Significantly more patients treated with rivastigmine withdrew from treatment for any reason than those treated with placebo (P=0.02).
Emre et al.[114] (2014) Rivastigmine capsules 6 mg twice daily vs rivastigmine patch 9.5 mg/24 hours	OL, PRO, RCT Patients 50 to 85 years of age with mild-to-moderately severe Parkinson disease dementia, which developed at least one year after Parkinson's disease was diagnosed	N=583 76 weeks	Primary: Incidence of predefined adverse events due to worsening Parkinson's disease motor symptoms (tremor, rigidity, bradykinesia, and falls) and discontinuation rate due to predefined	Primary: The incidence of adverse effects due to worsening motor symptoms in the capsule groups was 36.1% (95% CI, 30.6 to 41.8), with tremor the most commonly reported (24.5%; 95% CI, 19.7 to 29.8). Overall, 4.4% (95% CI, 2.4 to 7.4) of capsule-treated patients discontinued due to worsening motor symptoms. Secondary: The incidence of adverse effects due to worsening motor symptoms in the patch group (31.9%; 95% CI, 26.6 to 37.7) was similar to capsules. Fewer patients experienced tremor with patch (9.7%; 95% CI, 6.6 to 13.7) compared to capsules. The incidences of bradykinesia, rigidity, and fall

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			potential adverse effects with capsules Secondary: Same as primary but with patch Efficacy: Mattis Dementia Rating Scale, ADCS-ADL, NPI-10	were similar between groups. The incidence of discontinuation due to worsening of motor symptoms was 2.4% (95% CI, 1.0 to 4.9) with patch. Efficacy: Improvements on Mattis Dementia Rating Scale and NPI-10 from baseline were observed in both groups at weeks 24 and 52. Deterioration in ADCS-ADL score from baseline was observed in both groups at all time points. The size of initial improvement on the Mattis Dementia Rating Scale and NPI-10 gradually declined in both groups; decline was greater in the patch group. In the overall population, there was a statistically significant difference in favor of capsules compared with patch at weeks 24 to 76 for MDRS; weeks 52 and 76 for ADCS-ADL; and weeks 24 and 76 for NPI-10.

Study abbreviations: AC=active control, CI=confidence interval, DB=double blind, DD=double dummy, ER=extended release, HR=hazard ratio, IR=immediate release, ITT=intent to treat, LOCF=last observation carried forward, MA=meta-analysis, MC=multicenter, NS=not significant, OL=open label, OR=odds ratio, OS=observational study, PC=placebo controlled, PG=parallel group, PP=per protocol, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SB=Single-blind, WMD=weighted mean difference
Efficacy Measures Key: ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive subscale, ADAS-cog/10=10-item cognitive subscale of the Alzheimer's Disease Assessment Scale, ADAS-cog/11=11-item cognitive subscale of the Alzheimer's Disease Assessment Scale, ADAS-cog/13=13-item cognitive subscale of the Alzheimer's Disease Assessment Scale, ADAS-cog/memory=Alzheimer's Disease Assessment Scale-Cognitive/Memory, ADAS-noncog=Alzheimer Disease Assessment Scale-Noncognitive, ADCPQ=Alzheimer's Disease Caregiver Preference Questionnaire, ADCS-ADL=Alzheimer's Disease Cooperative Study-Activities of Daily Living scale, ADCS-ADL-MCI= Alzheimer's Disease Cooperative Study-Activities of Daily Living-Mild Cognitive Impairment scale, ADCS-ADL-sev=Alzheimer Disease Cooperative Study-Activities of Daily Living-severe version, ADCS-CGIC=Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change, ADL=Activity of Daily Living, ApoE=apolipoprotein E, ARIA-E=amyloid related imaging abnormalities-edema, BADLS=Bristol Activities of Daily Living Scale, BEHAV-AD=Behavioral Pathology in Alzheimer's Disease Rating Scale, BGP=Behavioral Rating Scale for Geriatric Patients, BrADL=Bristol Activities of Daily Living Scale, CBQ=Caregiver Burden Questionnaire, CDR=Cognitive Drug Research, CDR-SB=Clinical Dementia Rating Scale-Sum of Boxes, CGA-NPI=Caregiver-Administered Neuropsychiatric Inventory, CGI-C=Clinical Global Impression of Change, CGI-I=Clinical Global Impression of Improvement scale, CIBIC=Clinician Interview-Based Impression of Change Scale, CIBIC-Plus=Clinician's Interview-Based Impression of Change Plus Caregiver Input, CMAI-K=Cohen Mansfield Agitation Inventory-Korean type, DAD=Disability Assessment, D-KEFS=Delis-Kaplan Executive Function System, ECG=electrocardiogram, FAB=Frontal Assessment Battery, FAST=Functional Assessment Staging, GBS=Gottfried-Bråne-Steen scale, GDS=Global Deterioration Scale, IADL=Instrumental Activity of Daily Living, IDDD=Interview for Deterioration in Daily Functioning Activities in Dementia, K-MMSE=Korean Mini-Mental Status Exam, MDS-ADL=Minimum Data Set-Activities of Daily Living, MMSE=Mini-Mental Status Exam, M-NCAS=Modified Nursing Care Assessment Scale, NPI=Neuropsychiatric Inventory, NPI-10=10-item Neuropsychiatric Inventory, QOL=quality of life, QoLS=Quality of Life Scale, PDS=Progressive Deterioration Scale, PET=positron emission tomography, RUSP=Resource Utilization for Severe Alzheimer Disease Patients, SIB=Severe Impairment Battery, SUVR=standardized uptake value ratio, UPDRS=Unified Parkinson's Disease Rating Scale

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
The cholinesterase inhibitors exhibit similar pharmacologic properties, and evidence from comparative studies support a switch strategy when patients are intolerant to one drug or when a therapeutic dose cannot be reached.[115] Gauthier et al. reported that when switched from donepezil to rivastigmine, approximately 50% of those who had adverse events or a lack of efficacy with donepezil tolerated or responded well to rivastigmine.[116] Wilkinson et al. found no difference in tolerability when patients were switched from donepezil to galantamine using either a four-day washout period or a seven-day washout period.[117] Sadowsky et al. evaluated immediate switch (no washout) or delayed switch (seven-day washout) from oral donepezil to transdermal rivastigmine following a four-week treatment period with donepezil.[118] The authors found that the rates of discontinuation due to any reason or adverse events were similar between the treatment groups. They concluded that both switch strategies were safe and well tolerated. Sakka et al. evaluated patients with moderate-to-severe Alzheimer's disease who were switched to donepezil after experiencing a treatment failure or intolerance with memantine.[119] The authors concluded that donepezil was effective and well tolerated in patients who discontinued memantine monotherapy, including those patients with previous exposure to cholinesterase inhibitors. A post-hoc analysis of five-month trial data with galantamine demonstrated that patients had similar efficacy outcomes, whether or not they had received prior anticholinesterase therapy, suggesting that a previous failure did not predict response to galantamine.[120]

Impact on Physician Visits
Fillenbaum et al. evaluated the frequency of outpatient visits for patients with Alzheimer's disease.[121] Outpatient visit ranged from 81 to 95% and was not related to the stage of dementia or institutional status. Leibson et al. demonstrated that the onset of Alzheimer's disease is not associated with greater use of acute care services, nor is the high use of nursing home care offset by fewer emergency room or hospital encounters.[122] Clark et al. evaluated a telephone intervention program where healthcare professionals work with patients and caregivers to determine resources within the family of an Alzheimer's patient.[123] Alzheimer's patients in the program felt less embarrassed and isolated because of their memory problems and reported less problems coping with their disease. Intervention patients with more severe impairment had fewer physician visits, were less likely to have an emergency room visit or hospital admission, and had decreased depression and strain. Wimo et al. demonstrated that the use of memantine in patients with moderate-to-severe Alzheimer's disease was associated with less total caregiver time compared to placebo.[124] There were also fewer patients institutionalized at week 28 in the memantine group compared to placebo.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 10. Relative Cost of the Alzheimer's Agents

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Parasympathomimetic (Cholinergic Agents)				
Donepezil	orally disintegrating tablet, tablet, transdermal patch	Adlarity®, Aricept®*	$$$$$	$
Galantamine	extended-release capsule, solution, tablet	N/A	$$$$$	$$
Rivastigmine	capsule, solution, transdermal patch	Exelon®*	$$$$$	$$
Central Nervous System Agents, Miscellaneous				
Aducanumab-avwa	injection	Aduhelm®	$$$$$	N/A
Lecanemab-irmb	injection	Leqembi®	$$$$$	N/A
Memantine	extended-release capsule, solution, tablet	Namenda®*, Namenda® XR*	$$$$$	$
Combination Products				
Memantine and donepezil	extended-release capsule	Namzaric®	$$$$$	N/A

*Generic is available in at least one dosage form or strength.
N/A=Not available.

X. Conclusions

The cholinesterase inhibitors are approved for the treatment of mild-to-moderate Alzheimer's disease. Donepezil is also approved for the treatment of severe disease. The N-Methyl-D-aspartate (NMDA) receptor antagonist, memantine, has only been approved for the treatment of moderate-to-severe Alzheimer's disease. Although these agents provide symptomatic benefit, they have not been shown to delay the progression of neurodegeneration. Aducanumab-avwa is an amyloid beta-directed antibody and is the first disease modifying therapy approved for the treatment of Alzheimer's disease. Aducanumab received FDA approval based on a surrogate endpoint (reduction in amyloid-β plaques) and has not yet been shown to provide a clinical benefit. Lecanemab-irmb is the second amyloid beta-directed antibody. It received accelerated approval in January 2023 and was then converted to traditional approval in July 2023.[125] All products with the exception of memantine-donepezil, aducanumab-avwa, and lecanemab-irmb are available in a generic formulation. Aducanumab-avwa will be discontinued by its manufacturer in 2024.[126]

There are several guidelines which discuss the role of these agents in the management of Alzheimer's disease.[14-17] The primary goal of treatment is to delay the progression of symptoms and preserve functional ability. The use of a cholinesterase inhibitor may lead to modest improvements in some patients; therefore, it is appropriate to offer a trial of one of these agents for patients with mild-to-moderate disease.[14-17] In patients with Alzheimer's disease, treatment with cholinesterase inhibitors (donepezil, galantamine, or rivastigmine) should be considered at the time of diagnosis, taking into account expected therapeutic benefits and potential safety issues. In patients with moderate to severe Alzheimer's disease, treatment with memantine should be considered taking into account expected therapeutic benefits and potential safety issues.[14-15] Guidelines do not give preference to one agent over another and have not been updated to include the place in therapy for aducanumab-avwa or lecanemab-irmb. Clinicians should base the treatment decision on tolerability, adverse events, and ease of use.[14-17]

Numerous clinical trials have evaluated the efficacy and safety of the cholinesterase inhibitors and memantine. Several outcomes have been assessed (using more than 40 different instruments), including cognition, global function, behavior, and quality of life. There is consistent evidence from well-designed studies that donepezil, galantamine, rivastigmine, and memantine positively affect cognition and global function, although the improvements are modest. The findings are less consistent for other outcomes, including behavior and quality of life. In most cases, the duration of these clinical trials was less than one year. Thus, there is insufficient evidence to determine the optimal duration of therapy.[15]

There are relatively few studies that directly compare the efficacy and safety of the Alzheimer's agents. Most of the trials have compared active treatment to placebo or no treatment. The studies also differ with regards to

design, patient population, and treatment duration, which make it difficult to directly compare the results.[18-114] Leqembi's (lecanemab-irmb) traditional approval is based on Phase 3 data from the Clarity AD clinical trial, in which lecanemab met its primary endpoint of global cognitive and functional scale, Clinical Dementia Rating Sum of Boxes (CDR-SB). Lecanemab treatment reduced clinical decline on CDR-SB by 27% at 18 months compared to placebo.[108,125] This agent as well as aducanumab carries a boxed warning for amyloid related imaging abnormalities. Monoclonal antibodies directed against aggregated forms of beta amyloid can cause amyloid related imaging abnormalities (ARIA), characterized as ARIA with edema (ARIA-E) and ARIA with hemosiderin deposition (ARIA-H). Incidence and timing of ARIA vary among treatments. ARIA usually occurs early in treatment and is usually asymptomatic, although serious and life-threatening events rarely can occur. Serious intracerebral hemorrhages, some of which have been fatal, have been observed in patients treated with this class of medications.[12,13] Monitoring is needed for amyloid related imaging abnormalities, including an MRI prior to the 5th, 7th, and 14th infusions for Leqembi®.[13]

The Centers for Medicare & Medicaid Services (CMS) completed further evaluation of aducanumab (Aduhelm®), including stakeholder input. After extensive evaluation and review due to the limited clinical efficacy outcomes data, beyond that seen with surrogate marker evaluation, compared to placebo in clinical trials and the significant safety concerns, CMS published the final national coverage determination for aducanumab (Aduhelm®) on April 7, 2022. The final Medicare national coverage determination indicates coverage of FDA-approved monoclonal antibody therapies directed against amyloid for the treatment of Alzheimer's disease when provided in accordance with the extensive coverage criteria outlined for coverage with evidence development for patients who have a clinical diagnosis of mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease dementia, both with confirmed presence of amyloid beta pathology consistent with Alzheimer's disease. The guidance indicates that monoclonal antibodies directed against amyloid that are approved by FDA for the treatment of Alzheimer's disease based upon evidence of efficacy from a change in a surrogate endpoint (e.g., amyloid reduction), considered as reasonably likely to predict clinical benefit, may be covered in a randomized controlled trial conducted under an investigational new drug application. Additionally, monoclonal antibodies directed against amyloid that are approved by FDA for the treatment of Alzheimer's disease based upon evidence of efficacy from a direct measure of clinical benefit may be covered in CMS-approved prospective comparative studies, that meet specific protocol and analysis requirements outlined by CMS.[127] CMS has created a "Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease CED Study Registry" which must be used (or another CMS-approved study) to get Medicare payment for treating patients with Leqembi®.[128]

There is insufficient evidence to support that one brand Alzheimer's agent is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process. Because aducanumab and lecanemab have narrow indications with limited usage, and very specific criteria must be met prior to initiating therapy, these agents should be managed through the "preferred with clinical criteria" program if a preferred agent is designated.

Therefore, all brand Alzheimer's agents within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand Alzheimer's agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

Aducanumab-avwa should not be placed in preferred status regardless of cost.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Skin and Mucus Membrane Immunomodulators
AHFS Class 849200
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I. Overview

The skin and mucus membrane immunomodulators are used for a variety of inflammatory and immunologic conditions. These agents achieve their therapeutic effect via several different mechanisms of action. The majority of agents inhibit the effect of proinflammatory cytokines, specifically interleukins (ILs) or tumor necrosis factor (TNF)-α. IL inhibitors include Bimzelx® (bimekizumab-bkzx) Siliq® (brodalumab), Dupixent® (dupilumab), Tremfya® (guselkumab), Taltz® (ixekizumab), Skyrizi® (risankizumab-rzaa), Spevigo® (spesolimab-sbzo), Ilumya® (tildrakizumab-asmn), Adbry® (tralokinumab-ldrm), and Stelara® (ustekinumab).[1-13]

The ILs that are targeted by immunomodulator agents include IL-1, IL-4, IL-6, IL-12, IL-13, IL-17A, IL-23, and IL-36, which are involved in inflammatory and immune responses. Ixekizumab is an IL-17A antagonist. Bimekizumab is an IL-17A and F antagonist. Brodalumab antagonizes the interleukin-17 receptor A (IL-17RA) pathway. Tildrakizumab, risankizumab, and guselkumab are IL-23 antagonists. Spesolimab is an IL-36 receptor antagonist. Ustekinumab is an IL-12 and IL-23 antagonist. Tralokinumab is an IL-13 antagonist. Dupilumab inhibits IL-4 and IL-13 by specifically binding to the IL-4Rα subunit shared by the IL-4 and IL-13 receptor complexes.[1-13]

Deucravacitinib is a tyrosine kinase 2 (TYK2) inhibitor, where TYK2 is an enzyme belonging to the Janus kinase (JAK) family. The precise mechanism linking the inhibition of TYK2 enzyme to therapeutic effectiveness in the treatment of adults with moderate-to-severe plaque psoriasis is not currently known.[1-13]

Because many of these agents are biologics made from living organisms and are extremely difficult to duplicate, regulations to approve generic versions of these agents have been challenging to develop and implement. Congress, through the Biologics Price Competition and Innovation Act (BPCI Act) of 2009, created an abbreviated licensure pathway for biological products that were deemed to be biosimilar to or interchangeable with an FDA-approved biological reference product.[14] A biosimilar product is defined as a biological product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product. Currently, the FDA has approved many biosimilar products across a wide range of disease states.[14] Ustekinumab is the only drug in this review with an approved biosimilar product.

The skin and mucus membrane immunomodulators that are included in this review are listed in Table 1. No agents are available in a generic formulation.

Table 1. Skin and Mucus Membrane Immunomodulators Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Bimekizumab-bkzx	injection	Bimzelx®	none
Brodalumab	injection	Siliq®	none
Deucravacitinib	tablet	Sotyktu®	none
Dupilumab	injection	Dupixent®	none
Guselkumab	injection	Tremfya®	none
Ixekizumab	injection	Taltz®	none
Risankizumab-rzaa	injection	Skyrizi®	none
Spesolimab-sbzo	injection	Spevigo®	none
Tildrakizumab-asmn	injection	Ilumya®	none
Tralokinumab-ldrm	injection	Adbry®	none
Ustekinumab	injection	Stelara®	none

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the skin and mucus membrane immunomodulators are summarized in Table 2.

Table 2. Treatment Guidelines Using the Skin and Mucus Membrane Immunomodulators

Clinical Guideline	Recommendation(s)

Assessment of Spondyloarthritis International Society/European League Against Rheumatism: **2016 Update of the Assessment of Spondyloarthritis International Society/European League Against Rheumatism Recommendations for the Management of Axial Spondyloarthritis (2017)**[15]	• Treatment of axial spondyloarthritis (axSpA) should be tailored according to:
	  ○ Current manifestations of the disease (axial, peripheral, extra-articular symptoms and signs).
	  ○ Patient characteristics (comorbidities and psychosocial factors).
	• Disease monitoring of patients with axSpA should include: patient-reported outcomes, clinical findings, laboratory tests, and imaging, all with the appropriate instruments and relevant to the clinical presentation. The frequency of monitoring should be decided on an individual basis depending on symptoms, severity, and treatment.
	• Treatment should be guided according to a predefined treatment target.
	• Patients should be educated about axSpA and encouraged to exercise on a regular basis and stop smoking; physical therapy should be considered.
	• Nonsteroidal anti-inflammatory drugs (NSAIDs) up to the maximum dose, are recommended as first line drug treatment for patients suffering from pain and stiffness, taking risks and benefits into account. Continuous treatment with an NSAID is preferred for patients who respond well to NSAIDs if symptomatic otherwise.
	• Analgesics, such as paracetamol and opioid-(like) drugs, might be considered for residual pain after previously recommended treatments have failed, are contraindicated, and/or poorly tolerated.
	• Patients with purely axial disease should normally not be treated with conventional synthetic disease-modifying antirheumatic drug (DMARD); sulfasalazine may be considered in patients with peripheral arthritis. Biological DMARDS should be considered in patients with persistently high disease activity despite conventional treatments; current practice is to start with tumor necrosis factor inhibitor (TNFi) therapy.
	• If TNFi therapy fails, switching to another TNFi or interleukin-17 inhibitor therapy should be considered.
	• If a patient is in sustained remission, tapering of a biological DMARD can be considered.
	• Total hip arthroplasty should be considered in patients with refractory pain or disability and radiographic evidence of structural damage, independent of age. Spinal corrective osteotomy in specialized centers may be considered in patients with severe disabling deformity.
	• If a significant change in the course of the disease occurs, causes other than inflammation, such as a spinal fracture, should be considered and appropriate evaluation, including imaging, should be performed.

American College of Rheumatology/ Spondylitis Association of America/ Spondyloarthritis Research and Treatment Network: **Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic**	<u>Recommendations for adults with active ankylosing spondylitis (AS)</u>
	• Treatment with NSAIDs is recommended over no treatment with NSAIDs. Continuous treatment with NSAIDs is recommended over on-demand treatment with NSAIDs. No particular NSAID is recommended as a preferred choice.
	• In adults with active AS despite treatment with NSAIDs:
	  ○ Treatment with sulfasalazine, methotrexate or tofacitinib is recommended over no treatment with these medications. Sulfasalazine or methotrexate should be considered only in patients with prominent peripheral arthritis or when TNFi are not available.
	  ○ Treatment with TNFi is recommended over treatment with tofacitinib
	  ○ TNFi treatment is recommended over no treatment with TNFi. No TNF-α

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Axial Spondyloarthritis (2019)[16]	inhibitor is recommended as preferred. ○ Treatment with secukinumab or ixekizumab is recommended over no treatment with secukinumab or ixekizumab. ○ Treatment with TNFi is recommended over treatment with secukinumab or ixekizumab. ○ Treatment with secukinumab or ixekizumab is recommended over treatment with tofacitinib. ○ For those patients who have contraindications to TNFi, treatment with secukinumab or ixekizumab is recommended over treatment with sulfasalazine, methotrexate or tofacitinib. • In adults with active AS despite treatment with the first TNFi used: ○ Treatment with secukinumab or ixekizumab is recommended over treatment with a different TNFi in patients with primary nonresponse to TNFi. ○ Treatment with a different TNFi is recommended over treatment with a non- TNFi biologic agent in patients with secondary nonresponse to TNFi. ○ Switching to treatment with a biosimilar of the first TNFi is strongly not recommended. ○ Addition of sulfasalazine or methotrexate in favor of treatment with a new biologic is not recommended. • In adults with active AS, treatment with systemic glucocorticoids is strongly not recommended. • In adults with AS and isolated active sacroiliitis despite treatment with NSAIDs, treatment with locally administered parenteral glucocorticoids is recommended over no treatment with local glucocorticoids. • In adults with AS with stable axial disease and active enthesitis despite treatment with NSAIDs, treatment with locally administered parenteral glucocorticoids is recommended over no treatment with local glucocorticoids. Peri-tendon injections of Achilles, patellar, and quadriceps tendons should be avoided. • In adults with stable axial disease and active peripheral arthritis despite treatment with NSAIDs, treatment with locally administered parenteral glucocorticoids is recommended over no treatment with local glucocorticoids. • Treatment with physical therapy is recommended over no treatment with physical therapy. Active physical therapy interventions are recommended over passive physical therapy interventions. Land-based physical therapy interventions are recommended over aquatic therapy interventions. <u>Recommendations for adults with stable AS</u> • On-demand treatment with NSAIDS is recommended over continuous treatment with NSAIDs. • In adults receiving treatment with TNFi and NSAIDs, continuing treatment with TNFi alone is recommended compared to continuing both treatments. • In adults receiving treatment with TNFi and conventional synthetic antirheumatic drug, continuing treatment with TNFi alone is recommended over continuing both treatments. • In adults receiving treatment with a biologic, discontinuation of the biologic or tapering of the biologic dose as a standard approach is not recommended. • In adults receiving treatment with an originator TNFi, continuing treatment with the originator TNFi is recommended over mandated switching to its biosimilar. • Treatment with physical therapy over no treatment with physical therapy is recommended. <u>Recommendations for adults with active or stable AS</u> • In adults receiving treatment with TNFi, co-treatment with low-dose

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	methotrexate is not recommended. Recommendations for adults with active nonradiographic axSpA • Treatment with NSAIDs is recommended over no treatment or on-demand treatment with NSAIDs. No particular NSAID is recommended as the preferred choice. • In adults with nonradiographic axSpA despite treatment with NSAIDs: o Treatment with sulfasalazine, methotrexate or tofacitinib is recommended over no treatment with these medications. o Treatment with TNFi is recommended over no treatment with TNFi. No particular TNFi is recommended as the preferred choice. o Treatment with TNFi is recommended over treatment with tofacitinib. o Treatment with secukinumab or ixekizumab is recommended over no treatment with secukinumab or ixekizumab. o Treatment with TNFi is recommended over treatment with secukinumab or ixekizumab. o Treatment with secukinumab or ixekizumab is recommended over treatment with tofacitinib. o For those patients who have contraindications to TNFi, treatment with secukinumab or ixekizumab is recommended over treatment with sulfasalazine, methotrexate or tofacitinib. • In adults with primary nonresponse to the first TNFi used, switching to secukinumab or ixekizumab is recommended over switching to a different TNFi. • In adults with secondary nonresponse to the first TNFi used, switching to a different TNFi is recommended over switching to a non-TNFi biologic. • In adults with nonradiographic axSpA despite treatment with the first TNFi used: o Switching to treatment with a biosimilar of the first TNFi is strongly not recommended. o Addition of sulfasalazine or methotrexate in favor of treatment with a new biologic is not recommended in favor of treatment with a different biologic. • Treatment with systemic glucocorticoids is strongly not recommended. • In adults with isolated active sacroiliitis despite treatment with NSAIDs, treatment with local glucocorticoids is recommended over no treatment with local glucocorticoids. • In adults with active enthesitis despite treatment with NSAIDs, treatment with locally administered parenteral glucocorticoids is recommended over no treatment with local glucocorticoids. Peri-tendon injections of Achilles, patellar, and quadriceps tendons should be avoided. • In adults with active peripheral arthritis despite treatment with NSAIDs, using treatment with locally administered parenteral glucocorticoids is recommended over no treatment with local glucocorticoids. • Treatment with physical therapy is recommended over no treatment with physical therapy. Active physical therapy interventions are recommended over passive physical therapy interventions. Land-based physical therapy interventions are recommended over aquatic therapy interventions. Recommendations for adults with stable nonradiographic axSpA • On-demand treatment with NSAIDS is recommended over continuous treatment with NSAIDs. • In adults receiving treatment with TNFi and NSAIDs, continuing treatment with TNFi alone is recommended compared to continuing both treatments. • In adults receiving treatment with TNFi and conventional synthetic antirheumatic drug, continuing treatment with TNFi alone is recommended over

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	continuing both treatments. • In adults receiving treatment with a biologic, discontinuation of the biologic or tapering of the biologic dose as a standard approach is not recommended. • In adults receiving treatment with an originator TNFi, continuation of treatment with the originator TNFi is recommended over mandated switching to its biosimilar. Recommendations for adults with active or stable nonradiographic axSpA • In adults receiving treatment with TNFi, co-treatment with low-dose methotrexate is not recommended.
National Institute for Health and Clinical Excellence: **TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis (2016)**[17] Reaffirmed March 2019	• Adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab are recommended, within their marketing authorizations, as options for treating severe active ankylosing spondylitis in adults whose disease has responded inadequately to, or who cannot tolerate, NSAIDs. Infliximab is recommended only if treatment is started with the least expensive infliximab product. People currently receiving infliximab should be able to continue treatment with the same infliximab product until they and their clinician consider it appropriate to stop. • Adalimumab, certolizumab pegol, and etanercept are recommended, within their marketing authorizations, as options for treating severe non-radiographic axial spondyloarthritis in adults whose disease has responded inadequately to, or who cannot tolerate, NSAIDs. • The choice of treatment should be made after discussion between the clinician and the patient about the advantages and disadvantages of the treatments available. This may include considering associated conditions such as extra-articular manifestations. If more than one treatment is suitable, the least expensive (taking into account administration costs and patient access schemes) should be chosen. • The response to adalimumab, certolizumab pegol, etanercept, golimumab, or infliximab treatment should be assessed 12 weeks after the start of treatment. Treatment should only be continued if there is clear evidence of response, defined as: o a reduction in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score to 50% of the pre-treatment value or by 2 or more units and o a reduction in the spinal pain visual analogue scale (VAS) by 2 cm or more. • Treatment with another TNF-α inhibitor is recommended for people who cannot tolerate, or whose disease has not responded to, treatment with the first TNF-α inhibitor, or whose disease has stopped responding after an initial response. • When using BASDAI and spinal pain VAS scores, healthcare professionals should take into account any physical, sensory, or learning disabilities, or communication difficulties that could affect the responses to the questionnaires and make any adjustments they consider appropriate.
American College of Gastroenterology: **Management of Crohn's Disease in Adults (2018)**[18]	Mild-to-moderately severe disease/low-risk disease • Sulfasalazine is effective for treating symptoms of colonic Crohn's disease that is mild to moderately active (conditional recommendation, low level of evidence). • Oral mesalamine has not consistently been demonstrated to be effective compared with placebo for induction of remission and achieving mucosal healing in patients with active Crohn's disease and should not be used to treat patients with active Crohn's disease (strong recommendation, moderate level of evidence). • Controlled ileal release budesonide at a dose of 9 mg once daily is effective and should be used for induction of symptomatic remission for patients with mild-

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	to-moderate ileocecal Crohn's disease (strong recommendation, low level of evidence). • Metronidazole is not more effective than placebo as therapy for luminal inflammatory Crohn's disease and should not be used as primary therapy (conditional recommendation, low level of evidence). • Ciprofloxacin has shown similar efficacy to mesalamine in active luminal Crohn's disease but has not been shown to be more effective than placebo to induce remission in Crohn's disease and should not be used as therapy for luminal inflammatory Crohn's disease (conditional recommendation, very low level of evidence). • Antimycobacterial therapy has not been shown to be effective for induction or for maintenance of remission or mucosal healing in patients with Crohn's disease and should not be used as primary therapy (conditional recommendation, low level of evidence). • For patients with low risk of progression, treatment of active symptoms with anti-diarrheals, other non-specific medications, and dietary manipulation, along with careful observation for inadequate symptom relief, worsening inflammation, or disease progression, is acceptable (strong recommendation, very low level of evidence). <u>Moderate-to-severe disease/moderate-to-high-risk disease</u> • Oral corticosteroids are effective and can be used for short-term use in alleviating signs and symptoms of moderate to severely active Crohn's disease (strong recommendation, moderate level of evidence). • Conventional corticosteroids do not consistently achieve mucosal healing and should be used sparingly (weak recommendation, low level of evidence). • Azathioprine (at doses of 1.5 to 2.5 mg/kg/day) and 6-mercaptopurine (at doses of 0.75 to 1.5 mg/kg day) are not more effective than placebo to induce short-term symptomatic remission and should not be used in this manner (strong recommendation, low level of evidence). • Thiopurines (azathioprine, 6-mercaptopurine) are effective and should be considered for use for steroid sparing in Crohn's disease (strong recommendation, low level of evidence). • Azathioprine and 6-mercaptourine are effective therapies and should be considered for treatment of patients with Crohn's disease for maintenance of remission (strong recommendation, moderate level of evidence). • Thiopurine methyltransferase (TPMT) testing should be considered before initial use of azathioprine or 6-mercaptopurine to treat patients with Crohn's disease (strong recommendation, low level of evidence). • Methotrexate (up to 25 mg once weekly IM or SC) is effective and should be considered for use in alleviating signs and symptoms in patients with steroid-dependent Crohn's disease and for maintaining remission (conditional recommendation, low level of evidence). • Anti-TNF agents (infliximab, adalimumab, certolizumab pegol) should be used to treat Crohn's disease that is resistant to treatment with corticosteroids (strong recommendation, moderate level of evidence). • Anti-TNF agents should be given for Crohn's disease refractory to thiopurines or methotrexate (strong recommendation, moderate level of evidence). • Combination therapy of infliximab with immunomodulators (thiopurines) is more effective than treatment with either immunomodulators alone or infliximab alone in patients who are naive to those agents (strong recommendation, high level of evidence). • For patients with moderately to severely active Crohn's disease and objective evidence of active disease, anti-integrin therapy (with vedolizumab) with or without an immunomodulator is more effective than placebo and should be

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	considered to be used for induction of symptomatic remission in patients with Crohn's disease (strong recommendation, high level of evidence). • Natalizumab is more effective than placebo and should be considered to be used for induction of symptomatic response and remission in patients with active Crohn's disease (strong recommendation, high level of evidence). • Natalizumab should be used for maintenance of natalizumab-induced remission of Crohn's disease only if serum antibody to John Cunningham (JC) virus is negative. Testing for anti-JC virus antibody should be repeated every 6 months and treatment stopped if the result is positive. (strong recommendation, moderate level of evidence). • Ustekinumab should be given for moderate-to-severe Crohn's disease patients who failed previous treatment with corticosteroids, thiopurines, methotrexate, or anti-TNF inhibitors or who have had no prior exposure to anti-TNF inhibitors (strong recommendation, high level of evidence). • Cyclosporine, mycophenolate mofetil, and tacrolimus should not be used for Crohn's disease (strong recommendation, moderate level of evidence). <u>Severe/fulminant disease</u> • Intravenous corticosteroids should be used to treat severe or fulminant Crohn's disease (conditional recommendation, moderate level of evidence). • Anti-TNF agents (infliximab, adalimumab, certolizumab pegol) can be considered to treat severely active Crohn's disease (strong recommendation, moderate level of evidence). • Infliximab may be administered to treat fulminant Crohn's disease (conditional recommendation, low level of evidence). <u>Perianal/fistulizing disease</u> • Infliximab is effective and should be considered in treating perianal fistulas in Crohn's disease (strong recommendation, moderate level of evidence). • Infliximab may be effective and should be considered in treating enterocutaneous and rectovaginal fistulas in Crohn's disease (strong recommendation, moderate level of evidence). • Adalimumab and certolizumab pegol may be effective and should be considered in treating perianal fistulas in Crohn's disease (strong recommendation, low level of evidence). • Thiopurines (azathioprine, 6-mercaptopurine) may be effective and should be considered in treating fistulizing Crohn's disease (strong recommendation, low level of evidence). • Tacrolimus can be administered for short-term treatment of perianal and cutaneous fistulas in Crohn's disease (strong recommendation, moderate level of evidence). • Antibiotics (imidazoles) may be effective and should be considered in treating simple perianal fistulas (strong recommendation, moderate level of evidence). • The addition of antibiotics to infliximab is more effective than infliximab alone and should be considered in treating perianal fistulas (strong recommendation, moderate level of evidence). • Drainage of abscesses (surgically or percutaneously) should be undertaken before treatment of fistulizing Crohn's disease with anti-TNF agents (conditional recommendation, very low level of evidence). • Placement of setons increases the efficacy of infliximab and should be considered in treating perianal fistulas (strong recommendation, moderate level of evidence). <u>Maintenance Therapy of Luminal Crohn's Disease</u> • Once remission is induced with corticosteroids, a thiopurine or methotrexate

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	should be considered (strong recommendation, moderate level of evidence). • Patients who are steroid dependent should be started on thiopurines or methotrexate with or without anti-TNF therapy (strong recommendation, moderate level of evidence). • Oral 5-aminosalicylic acid has not been demonstrated to be effective for maintenance of medically induced remission in patients with Crohn's disease, and is not recommended for long-term treatment (strong recommendation, moderate level of evidence). • Corticosteroids are not effective for maintenance of medically induced remission in Crohn's disease and should not be used for long-term treatment (strong recommendation, moderate level of evidence). • Budesonide should not be used to maintain remission of Crohn's disease beyond 4 months (strong recommendation, moderate level of evidence). • Anti-TNF therapy, specifically infliximab, adalimumab, and certolizumab pegol, should be used to maintain remission of anti-TNF-induced remission (strong recommendation, high level of evidence). • Anti-TNF monotherapy is effective at maintaining anti-TNF induced remission, but because of the potential for immunogenicity and loss of response, combination with azathioprine/6-mercaptopurine or methotrexate should be considered (strong recommendation, moderate level of evidence). • Vedolizumab should be used for maintenance of remission of vedolizumab-induced remission of Crohn's disease (conditional recommendation, moderate level of evidence). • Natalizumab should be considered for maintaining remission of natalizumab-induced remission of Crohn's disease patients only if John Cunningham (JC) virus is negative (conditional recommendation, moderate level of evidence). • Ustekinumab should be used for maintenance of remission of ustekinumab-induced response of Crohn's disease (conditional recommendation, moderate level of evidence). <u>Postoperative Crohn's Disease</u> • All patients who have Crohn's disease should quit smoking (conditional recommendation, very low level of evidence). • Mesalamine is of limited benefit in preventing postoperative Crohn's disease, but in addition to no treatment is an option for patients with an isolated ileal resection and no risk factors for recurrence (conditional recommendation, moderate level of evidence). • Imidazole antibiotics (metronidazole and ornidazole) at doses between 1 and 2 g/day can be used after small intestinal resection in Crohn's disease patients to prevent recurrence (conditional recommendation, low level of evidence). • Thiopurines may be used to prevent clinical and endoscopic recurrence and are more effective than mesalamine or placebo. However, they are not effective at preventing severe endoscopic recurrence (strong recommendation, moderate level of evidence). • In high-risk patients, anti-TNF agents should be started within four weeks of surgery in order to prevent postoperative Crohn's disease recurrence (conditional recommendation, low level of evidence). • Although data are lacking in postoperative Crohn's disease, anti-TNF therapy should be combined with an immunomodulator to decrease immunogenicity and decrease loss of response (conditional recommendation, very low level of evidence).
National Institute for Health and Clinical Excellence: **Crohn's Disease**	<u>Monotherapy</u> • Offer monotherapy with a conventional glucocorticosteroid (prednisolone, methylprednisolone or intravenous hydrocortisone) to induce remission in people with a first presentation or a single inflammatory exacerbation of

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Management (2019)[19]	Crohn's disease in a 12-month period.
	• Consider enteral nutrition as an alternative to a conventional glucocorticosteroid to induce remission for:
	  ○ Children in whom there is concern about growth or side effects.
	  ○ Young people in whom there is concern about growth.
	• In people with one or more of distal ileal, ileocecal or right-sided colonic disease who decline, cannot tolerate or in whom a conventional glucocorticosteroid is contraindicated, consider budesonide for a first presentation or a single inflammatory exacerbation in a 12-month period.
	• In people who decline, cannot tolerate or in whom glucocorticosteroid treatment is contraindicated, consider 5-aminosalicylate (5-ASA) treatment for a first presentation or a single inflammatory exacerbation in a 12-month period.
	• Do not offer budesonide or 5-ASA treatment for severe presentations or exacerbations.
	• Do not offer azathioprine, mercaptopurine or methotrexate as monotherapy to induce remission.
	
	<u>Combination therapy</u>
	• Consider adding azathioprine or mercaptopurine to a conventional glucocorticosteroid or budesonide to induce remission of Crohn's disease if:
	  ○ There are two or more inflammatory exacerbations in a 12-month period, or
	  ○ The glucocorticosteroid dose cannot be tapered.
	• Assess thiopurine methyltransferase (TPMT) activity before offering azathioprine or mercaptopurine. Do not offer azathioprine or mercaptopurine if TPMT activity is deficient (very low or absent). Consider azathioprine or mercaptopurine at a lower dose if TPMT activity is below normal but not deficient (according to local laboratory reference values).
	• Consider adding methotrexate to a conventional glucocorticosteroid or budesonide to induce remission in people who cannot tolerate azathioprine or mercaptopurine, or in whom TPMT activity is deficient, if:
	  ○ There are two or more inflammatory exacerbations in a 12-month period, or
	  ○ The glucocorticosteroid dose cannot be tapered.
	• Monitor the effects of azathioprine, mercaptopurine and methotrexate. Monitor for neutropenia in people taking azathioprine or mercaptopurine even if they have normal TPMT activity.
	
	<u>Infliximab and adalimumab</u>
	• Infliximab and adalimumab, within their licensed indications, are recommended as treatment options for adults with severe active Crohn's disease whose disease has not responded to conventional therapy (including immunosuppressive and/or corticosteroid treatments), or who are intolerant of or have contraindications to conventional therapy.
	• Infliximab or adalimumab should be given as a planned course of treatment until treatment failure (including the need for surgery), or until 12 months after the start of treatment, whichever is shorter. People should then have their disease reassessed to determine whether ongoing treatment is still clinically appropriate.
	• Treatment as described should normally be started with the less expensive drug. This may need to be varied for individuals because of differences in the method of administration and treatment schedules.
	• Options of monotherapy with one of these drugs or combined therapy should be discussed when starting infliximab or adalimumab.
	• Infliximab is recommended as a treatment option for people with active

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	fistulizing Crohn's disease whose disease has not responded to conventional therapy (including antibiotics, drainage and immunosuppressive treatments), or who are intolerant of or have contraindications to conventional therapy. • Infliximab should be given as a planned course of treatment until treatment failure (including the need for surgery) or until 12 months after the start of treatment, whichever is shorter. People should then have their disease reassessed to determine whether ongoing treatment is still clinically appropriate. • Treatment with infliximab or adalimumab should only be continued if there is clear evidence of ongoing active disease as determined by clinical symptoms, biological markers and investigation, including endoscopy if necessary. Specialists should discuss the risks and benefits of continued treatment with patients and consider a trial withdrawal from treatment for all patients who are in stable clinical remission. People who continue treatment with infliximab or adalimumab should have their disease reassessed at least every 12 months to determine whether ongoing treatment is still clinically appropriate. People whose disease relapses after treatment is stopped should have the option to start treatment again. • Infliximab is recommended for the treatment of people aged 6 to 17 years with severe active Crohn's disease whose disease has not responded to conventional therapy (including corticosteroids, immunomodulators and primary nutrition therapy), or who are intolerant of or have contraindications to conventional therapy. The need to continue treatment should be reviewed at least every 12 months. • Treatment with infliximab or adalimumab should only be started and reviewed by clinicians with experience of TNFi and of managing Crohn's disease. <u>Remission maintenance</u> • For patients that choose maintenance therapy, offer azathioprine or mercaptopurine as monotherapy to maintain remission when previously used with a conventional glucocorticosteroid or budesonide to induce remission or to maintain remission in patients not previously treated with these medications. • Consider methotrexate to maintain remission only in patients who: o Needed methotrexate to induce remission. o Did not tolerate azathioprine or mercaptopurine for maintenance. o Contraindicated to azathioprine or mercaptopurine. • Do not offer conventional glucocorticosteroids or budesonide to maintain remission. <u>Remission maintenance following surgery</u> • To maintain remission in people with ileocolonic Crohn’s disease who have had complete macroscopic resection within the last three months, consider azathioprine in combination with up to three months post-operative metronidazole. Azathioprine alone should be considered for patients who cannot tolerate metronidazole. • Effects of azathioprine and metronidazole should be monitored, including neutropenia in patients taking azathioprine even if they have normal TPMT. • Biologics should not be offered to maintain remission after complete macroscopic resection of ileocolonic Crohn's disease. For patients who have had surgery and started taking biologics already, continue with their current treatment until both they and their healthcare professional agree it is appropriate to change.
European League Against Rheumatism: **Recommendations For The Management Of Psoriatic Arthritis With**	• Treatment should be aimed at reaching the target of remission or, alternatively, low disease activity, by regular disease activity assessment and appropriate adjustment of therapy. • NSAIDs may be used to relieve musculoskeletal signs and symptoms.

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Pharmacological Therapies: 2019 Update (2019)[20]	• Local injections of glucocorticoids should be considered as adjunctive therapy in psoriatic arthritis; systemic glucocorticoids may be used with caution at the lowest effective dose. • In patients with polyarthritis, a conventional synthetic DMARD should be initiated rapidly, with methotrexate preferred in those with relevant skin involvement. • In patients with monoarthritis or oligoarthritis, particularly with poor prognostic factors such as structural damage, high erythrocyte sedimentation rate/C reactive protein, dactylitis or nail involvement, a conventional synthetic DMARD should be considered. • In patients with peripheral arthritis and an inadequate response to at least one conventional synthetic DMARD, therapy with a biological DMARD should be commenced; when there is relevant skin involvement, an interleukin-17 inhibitor or interleukin-12/23 inhibitor may be preferred. • In patients with peripheral arthritis and an inadequate response to at least one conventional synthetic DMARD and at least one DMARD, or when a biological DMARD is not appropriate, a JAK inhibitor may be considered. • In patients with mild disease and an inadequate response to at least one conventional synthetic DMARD†, in whom neither a biological DMARD nor a JAK inhibitor is appropriate*, a phosphodiesterase-4 inhibitor may be considered. • In patients with unequivocal enthesitis and insufficient response to NSAIDs or local glucocorticoid injections, therapy with a biological DMARD should be considered. • In patients with predominantly axial disease which is active and has insufficient response to NSAIDs, therapy with a biological DMARD should be considered, which according to current practice is a TNFi; when there is relevant skin involvement, interleukin-17 inhibitor may be preferred. • In patients who fail to respond adequately to, or are intolerant of a biological DMARD, switching to another biological DMARD or targeted synthetic DMARD should be considered, including one switch within a class. • In patients in sustained remission, cautious tapering of DMARDs may be considered.
American Academy of Dermatology/National Psoriasis Foundation: **Joint Guidelines of Care for the Management and Treatment of Psoriasis with Biologics (2019)[21]**	<u>Biologics</u> • Four TNFi's are FDA-approved for the treatment of moderate-to-severe psoriasis: adalimumab, etanercept, infliximab, and certolizumab. • Seven interleukin antagonists are FDA-approved for the treatment of moderate-to-severe psoriasis: ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, tildrakizumab, and risankizumab. • Etanercept and adalimumab are recommended as monotherapy, and can be combined with topical therapies, acitretin, methotrexate, apremilast, cyclosporine, and phototherapy to augment efficacy. • Infliximab is recommended as monotherapy, and can be combined with topical therapies, acitretin, methotrexate, and apremilast to augment efficacy. • Ustekinumab is recommended as monotherapy, and can be combined with topical therapies, acitretin, methotrexate, apremilast, cyclosporine, and phototherapy to augment efficacy. Ustekinumab is less effective than TNF-α inhibitors for psoriatic arthritis. • Secukinumab, ixekizumab, brodalumab, guselkumab, tildrakizumab, and risankizumab are recommended as monotherapy. • All biologics may lose efficacy in patients who initially respond favorably to medication (secondary failure). • The necessity of repeating loading doses depends on disease severity and how many doses were missed. Retreatment after discontinuation may result in a small percentage of patients not being able to recapture previous robust level of

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	response. • If clinically needed, all therapies may be switched with a different biologic agent with the possibility of improved efficacy, safety, and/or tolerability. • Etanercept is the only biologic approved for plaque psoriasis in children aged 4 to 17 years, whereas ustekinumab is approved for plaque psoriasis in adolescents aged 12 to 17 years.
American Academy of Dermatology/National Psoriasis Foundation: **Joint Guidelines of Care for the Management and Treatment of Psoriasis with Systemic Nonbiologic Therapies (2020)**[22]	• Methotrexate is recommended for the treatment of moderate to severe psoriasis in adults. • Methotrexate is less effective than adalimumab and infliximab for cutaneous psoriasis. • Methotrexate is efficacious for treatment of psoriatic arthritis (peripheral arthritis, but not for axial involvement); in psoriatic arthritis, the efficacy of methotrexate is lower than TNFi. • Methotrexate can be administered orally or subcutaneously. • Apremilast is recommended for the treatment of moderate to severe psoriasis in adults. • Cyclosporine is recommended for patients with severe, recalcitrant psoriasis. • Cyclosporine can be recommended for the treatment of erythrodermic, generalized pustular, and/or palmoplantar psoriasis. • Cyclosporine can be recommended as short-term interventional therapy in patients who flare up while on a pre-existing systemic therapy. • Acitretin can be recommended as monotherapy for plaque psoriasis. • Acitretin can be recommended for treatment of erythrodermic, pustular, and palmar plantar psoriasis. • Tofacitinib can be considered for treatment of moderate to severe psoriasis but is not currently FDA approved for that indication. • Dimethyl fumarate is approved in the United States for treatment of relapsing forms of multiple sclerosis. It can be recommended for psoriasis. • Although rarely necessary for psoriasis, systemic immunosuppressants and antimetabolites, including hydroxyurea, mycophenolate mofetil, azathioprine, leflunomide, tacrolimus, and thioguanine, may have value for this disease in certain instances.
Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA): **Updated treatment recommendations for psoriatic arthritis (2021)**[23]	Peripheral Disease: • NSAIDs and intra-articular and oral glucocorticoids are conditionally recommended for relieving symptoms of peripheral arthritis as per the 2015 recommendation, as no new relevant data were identified. • For treatment-naive patients, there remains a low level of evidence to support the use of conventional synthetic DMARDs. However, in • view of supportive observational data and universal accessibility, the use of csDMARDs (methotrexate, sulfasalazine or leflunomide) is strongly recommended. • In many circumstances, csDMARDs can be used as first-line therapy, with regular assessment of clinical response (every 12 to 24 weeks) and early escalation of therapy (between 12 and 24 weeks) advised as necessary. • New, high-quality data support the superiority of TNF inhibitors over csDMARDs as first-line therapy, particularly in patients with early disease. • For all RCTs reviewed for phosphodiesterase 4 inhibitors (PDE4i), TNF inhibitors, IL-17 inhibitors, IL-12/23 inhibitors, IL-23 inhibitors and JAK inhibitors, there were no differences in efficacy for these treatment options in subgroups of patients with or without concurrent csDMARDs. • For patients with an inadequate response to csDMARDs, high-quality evidence supports the use of TNF inhibitors, IL-17 inhibitors, IL-23 inhibitors and JAK inhibitors; and moderate-quality evidence supports IL-12/23 inhibitors or PDE4 inhibitors being superior to placebo. • Similar magnitudes of effect sizes for efficacy were observed across RCTs for

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	TNF inhibitors, IL-17 inhibitors, IL-23 inhibitors and JAK inhibitors compared with placebo, whereas effect sizes for PDE4 inhibitors and IL-12/23 inhibitors seemed to be lower. These classes of drugs are all strongly recommended on the basis of this evidence. Axial Disease: • For patients with axial symptoms who have not responded to treatment with NSAIDs, physiotherapy and/or sacroiliac joint glucocorticoid injections (when appropriate), initiation of a targeted therapy is strongly recommended. TNF inhibition and IL-17 inhibition have demonstrated efficacy in both radiographic and non-radiographic axSpA and were recommended for axial PsA in the previous GRAPPA recommendations. • Since the 2015 recommendations, several phase II and phase II–III RCTs have demonstrated the efficacy of the JAK inhibitors tofacitinib, upadacitinib and filgotinib in ankylosing spondylitis. Data from a phase III study of tofacitinib in ankylosing spondylitis published in 2021 confirm this efficacy. Extrapolating from the evidence in axSpA, we recommend these agents for axial PsA as well. • As IL-17 inhibitors have shown efficacy and have been approved for use in the treatment of axSpA, these agents are strongly recommended for axial PsA. • Although IL-12/23 inhibitors and IL-23 inhibitors have not demonstrated efficacy in ankylosing spondylitis, post hoc analyses from the trials of ustekinumab and guselkumab in patients who have had axial symptoms suggest that these agents might be effective in axial PsA. Enthesitis: • Classes of advanced therapies found to be effective and thus strongly recommended as treatment options for active enthesitis in patients with PsA include TNF inhibitors, IL-17 inhibitors, IL-12/23 inhibitors, IL-23 inhibitors, JAK inhibitors and PDE4 inhibitors. • Despite novel information about the comparative efficacy of different classes of medications emerging from head-to-head studies, including comparisons of IL-17 inhibitors with TNF inhibitors, methotrexate with TNF inhibitors, and IL-12/23 inhibitors with TNF inhibitors, none of the evaluated classes of medications was found to have clear and consistent superiority over the other. Therefore, none of the medication classes detailed above was prioritized for the treatment of enthesitis in the recommendations. Dactylitis: • The IL-17 inhibitors secukinumab, ixekizumab and brodalumab demonstrated superior efficacy compared with placebo for improving dactylitis signs and symptoms in RCTs; another IL-17 inhibitor, bimekizumab, is being studied. • In RCTs the IL-23 inhibitors guselkumab and risankizumab were found to be effective for dactylitis. • A strong recommendation was established for the use of TNF inhibitors, IL-12/23 inhibitors, IL-23 inhibitors, IL-17 inhibitors, JAK inhibitors and PDE4 inhibitors, and a conditional recommendation was established for the use of CTLA4-Ig in the treatment of dactylitis in PsA.
American College of Gastroenterology: **Ulcerative Colitis in Adults (2019)**[24]	Induction of remission in mildly active ulcerative colitis (UC) • In patients with mildly active ulcerative proctitis, rectal 5-ASA therapies are recommended. • In patients with mildly active left-sided colitis, rectal 5-ASA enemas are recommended over rectal steroids for induction of remission. • In patients with mildly active left-sided UC, rectal 5-ASA enemas are recommended combined with oral 5-ASA compared with oral 5-ASA therapy alone for induction of remission.

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	• In patients with mildly active left-sided UC who are intolerant or nonresponsive to oral and rectal 5-ASA at appropriate doses oral budesonide MMX is recommended for induction of remission. • In patients with mildly active extensive colitis, oral 5-ASA is recommended to induce remission. • In patients with UC of any extent who fail to respond to 5-ASA therapy, oral systemic corticosteroids are recommended to induce remission. • In patients with mildly active UC who fail to reach remission with appropriately dosed 5-ASA changing to an alternate 5-ASA formulation to induce remission is not recommended. Alternative therapeutic classes should be considered (conditional recommendation, low quality of evidence). • In patients with mildly active UC of any extent, using a low dose of 5-ASA compared with a higher dose is recommended, as there is no difference in the remission rate. • In patients with mildly to moderately active UC not responding to oral 5-ASA, the addition of budesonide MMX to induce remission is recommended. • In patients with mildly to moderately active UC of any extent using 5-ASA to induce remission, either once-daily or more frequently dosed oral 5-ASA is recommended based on patient preference to optimize adherence. <u>Maintenance of remission in patients with previously mildly active UC</u> • In patients with mildly active ulcerative proctitis, rectal 5-ASA is recommended. • In patients with mildly active left-sided or extensive UC, oral 5-ASA therapy is recommended. • Use of systemic corticosteroids for maintenance of remission in patients with UC is not recommended. <u>Induction of remission in moderately to severely active UC</u> • In patients with moderately active UC, oral budesonide MMX is recommended for induction of remission. • In patients with moderately to severely active UC of any extent, oral systemic corticosteroids are recommended to induce remission. • In patients with moderately to severely active UC, monotherapy with thiopurines or methotrexate is not recommended for induction of remission. • In patients with moderately to severely active UC, anti-TNF therapy using adalimumab, golimumab, or infliximab for induction of remission is recommended. • In patients with moderately to severely active UC who have failed 5-ASA therapy and in whom anti-TNF therapy is used for induction of remission, using 5-ASA for added clinical efficacy is not recommended. • When infliximab is used as induction therapy for patients with moderately to severely active UC, combination therapy with a thiopurine is recommended. • In patients with moderately to severely active UC, vedolizumab is recommended for induction of remission. • In patients with moderately to severely active UC who have previously failed anti-TNF therapy, vedolizumab is recommended for induction of remission. • In patients with moderately to severely active UC, tofacitinib is recommended to induce remission. • In patients with moderately to severely active UC who have previously failed anti-TNF therapy, tofacitinib is recommended for induction of remission. • In patients with moderately to severely active UC who are responders to anti-TNF therapy and now losing response, measuring serum drug levels and antibodies is recommended to assess the reason for loss of response.

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	Maintenance of remission in patients with previously moderately to severely active UC • In patients with previously moderately to severely active UC who have achieved remission but previously failed 5-ASA therapy and are now on anti-TNF therapy, using concomitant 5-ASA for efficacy of maintenance of remission is not recommended. • Use of systemic corticosteroids for maintenance of remission in patients with UC is not recommended. • For patients with previously moderately to severely active UC now in remission due to corticosteroid induction, thiopurines for maintenance of remission is recommended compared with no treatment or corticosteroids. • In patients with previously moderately to severely active UC now in remission, using methotrexate for maintenance of remission is not recommended. • Continuation of anti-TNF therapy using adalimumab, golimumab, or infliximab is recommended to maintain remission after anti-TNF induction in patients with previously moderately to severely active UC. • Continuation of vedolizumab to maintain remission is recommended in patients with previously moderately to severely active UC now in remission after vedolizumab induction. • Continuation of tofacitinib for maintenance of remission is recommended in patients with previously moderately to severely active UC now in remission after induction with tofacitinib.

The American Gastroenterological Association (AGA): **Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis (2020)**[25]	• In adult outpatients with moderate to severe ulcerative colitis, the AGA recommends using infliximab, adalimumab, golimumab, vedolizumab, tofacitinib, or ustekinumab over no treatment. (Strong recommendation, moderate quality evidence)
	• In adult outpatients with moderate to severe ulcerative colitis who are naïve to biologic agents, the AGA suggests using infliximab or vedolizumab rather than adalimumab, for induction of remission. (Conditional recommendation, moderate quality evidence)
	  ○ Patients, particularly those with less severe disease, who place higher value on the convenience of self-administered subcutaneous injection, and a lower value on the relative efficacy of medications, may reasonably chose adalimumab as an alternative.
	• In adult outpatients with moderate to severe ulcerative colitis who are naïve to biologic agents, the AGA recommends that tofacitinib only be used in the setting of a clinical or registry study. (No recommendation, knowledge gap)
	  ○ Updated FDA recommendations (July 26, 2019) on indications for use of tofacitinib in ulcerative colitis recommend its use only after failure of, or intolerance to TNF-α antagonists.
	• In adult outpatients with moderate to severe ulcerative colitis who have previously been exposed to infliximab, particularly those with primary nonresponse, the AGA suggests using ustekinumab or tofacitinib, rather than vedolizumab or adalimumab, for induction of remission. (Conditional recommendation, low quality evidence)
	  ○ Patients, particularly those with less severe disease, who place higher value on the potential safety of medications, and a lower value on the relative efficacy of medications, may reasonably chose vedolizumab as an alternative.
	• In adult outpatients with active moderate to severe ulcerative colitis, the AGA suggests against using thiopurine monotherapy for INDUCTION of remission. (Conditional recommendation, very low quality of evidence)
	• In adult outpatients with moderate to severe ulcerative colitis in remission, the AGA suggests using thiopurine monotherapy, rather than no treatment, for MAINTENANCE of remission. (Conditional recommendation low quality of

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	evidence) • In adult outpatients with moderate to severe ulcerative colitis, the AGA suggests against using methotrexate monotherapy for induction or maintenance of remission. (Conditional recommendation, low quality evidence) • In adult outpatients with active moderate to severe ulcerative colitis, the AGA suggests using biologic monotherapy (TNF-α antagonists, vedolizumab, ustekinumab) rather than thiopurine monotherapy for INDUCTION of remission. (Conditional recommendation, low quality evidence) • In adult outpatients with moderate to severe ulcerative colitis in remission, the AGA makes no recommendation in favor of, or against, using biologic monotherapy (TNF-α antagonists, vedolizumab, or ustekinumab), rather than thiopurine monotherapy for MAINTENANCE of remission. (No recommendation, knowledge gap) • In adult outpatients with moderate to severe ulcerative colitis, the AGA suggests combining TNF-α antagonists, vedolizumab, or ustekinumab with thiopurines or methotrexate, rather than biologic monotherapy. (Conditional recommendation, low quality evidence) o Patients, particularly those with less severe disease, who place higher value on lower risk of adverse events with biologic monotherapy, and lower value on the relative efficacy of combination therapy, may reasonably chose biologic monotherapy. • In adult outpatients with moderate to severe ulcerative colitis, the AGA suggests combining TNF-α antagonists, vedolizumab, or ustekinumab with thiopurines or methotrexate, rather than thiopurine monotherapy. (Conditional recommendation, low quality evidence) • In adult outpatients with moderate to severe ulcerative colitis, the AGA suggests early use of biologic agents with or without immunomodulator therapy, rather than gradual step up after failure of 5-ASA. (Conditional recommendation, very low quality evidence) o Patients, particularly those with less severe disease, who place higher value on the safety of 5-ASA therapy, and lower value on the efficacy of biologic agents, may reasonably choose gradual step therapy with 5-ASA therapy. • In adult outpatients with moderate to severe ulcerative colitis who have achieved remission with biologic agents and/or immunomodulators, or tofacitinib, the AGA suggests against continuing 5-ASA for induction and maintenance of remission. (Conditional recommendation, very low quality evidence) • In hospitalized adult patients with acute severe ulcerative colitis, the AGA suggests using intravenous methylprednisolone dose equivalent of 40 to 60 mg/d rather than higher doses of intravenous corticosteroids. (Conditional recommendation, very low quality evidence) • In hospitalized adult patients with acute severe ulcerative colitis without infections, the AGA suggests against adjunctive antibiotics. (Conditional recommendation, very low quality of evidence) • In hospitalized adult patients with acute severe ulcerative colitis refractory to intravenous corticosteroids, the AGA suggests using infliximab or cyclosporine. (Conditional recommendation, low quality evidence) In hospitalized adult patients with acute severe UC, refractory to intravenous corticosteroids, being treated with infliximab, the AGA makes no recommendation on routine use of intensive vs standard infliximab dosing. (No recommendation, knowledge gap)
European Academy of Dermatology and Venereology: **Consensus-based**	• Emollients should be prescribed in adequate amounts, and these should be used liberally and frequently, in a minimum amount of 250 g per week for adults. • Emollient bath oils and soap substitutes should also be used. Emollients with a

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European Guidelines for Treatment of Atopic Eczema (Atopic Dermatitis) in Adults and Children (2018)[26]	higher lipid content are preferable in wintertime. • A regular use of emollient has a short- and long-term steroid sparing effect in mild-to-moderate atopic eczema. An induction of remission with topical corticosteroids or topical calcineurin inhibitors is required first. • Topical corticosteroids are important anti-inflammatory drugs to be used in atopic eczema, especially in the acute phase. • Topical corticosteroids with an improved risk/benefit ratio are recommended in atopic eczema. • Diluted topical corticosteroids may be used under wet wraps for short-term periods in acute atopic eczema to increase their efficacy. • Proactive therapy (e.g., twice-weekly application in the long-term follow-up) may help to reduce relapses. • Proactive therapy with topical corticosteroids may be used safely for at least 20 weeks, which is the longest duration of trials. • Patient fear of side-effects of corticosteroids should be recognized and adequately addressed to improve adherence and avoid undertreatment. • Topical calcineurin inhibitors are important anti-inflammatory drugs to be used in atopic eczema. Instead of treating acute flares with topical calcineurin inhibitors, initial treatment with topical corticosteroids before switching to topical calcineurin inhibitors should be considered. • Topical calcineurin inhibitors are especially indicated in sensitive skin areas (face, intertriginous sites, anogenital area). • Proactive therapy with twice-weekly application of tacrolimus ointment may reduce relapses. • Effective sun protection should be recommended inpatients treated with topical calcineurin inhibitors. • Topical corticosteroids are recommended to control pruritus in the initial phase of atopic eczema exacerbation. • Topical calcineurin inhibitors are recommended to control pruritus in atopic eczema until clearance of eczema. • Topical polidocanol may be used to reduce pruritus in atopic eczema patients. • Routine clinical use of topical antihistamines including doxepin, topical cannabinoid receptor agonists, topical μ-opioid receptor antagonists or topical anaesthetics cannot be recommended as an adjuvant antipruritic therapy in atopic eczema. • There is not enough data available to recommend the use of capsaicin in management of itch in atopic eczema patients. • If emollients and anti-inflammatory topical preparations must be applied to the same location, the cream formulation should be applied first and only 15 minutes later the ointment formulation. • For routine treatment of flares once daily application of a potent topical corticosteroid is sufficient, usually for three to six days. • With mild disease activity, a small amount of topical corticosteroids two to three times weekly, associated with a liberal use of emollients, generally allows a good maintenance with SCORAD values below 15 to 20 (indicating mild disease). • The most constructive way to spare topical corticosteroids and avoid steroid-related side-effects is not to spare them during acute flares, but through consequent baseline emollient skin care combined with early anti-inflammatory intervention in order to stabilize the disease, and prevent treatment-intensive flares. • The two steroid-free topical calcineurin inhibitors, tacrolimus ointment and pimecrolimus cream, have demonstrated efficacy against placebo in clinical trials for short-term and long-term use. • Proactive tacrolimus ointment therapy has been shown to be safe and effective

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	for up to one year in reducing the number of flares and improving the quality of life in adult patients and children. • The anti-inflammatory potency of 0.1% tacrolimus ointment is similar to a topical corticosteroid with intermediate activity, while the latter is clearly more active than 1.0% pimecrolimus cream. • The topical calcineurin inhibitors do not induce skin atrophy like corticosteroids, which favors their use on delicate skin areas like the eyelids, perioral skin, genital areas, inguinal fold, and for topical long-term management. • Clinical and preclinical data do not indicate an increased risk of the induction of lymphoma or other types of malignancies, or photocarcinogenicity for topical calcineurin inhibitors, but since the continuous oral administration of the calcineurin inhibitor cyclosporine is associated with an increased photocarcinogenicity risk in solid organ transplant patients, UV protection, (e.g., with sunscreens) is recommended.
American Academy of Allergy, Asthma, and Immunology/ American College of Allergy, Asthma, and Immunology/Joint Council on Allergy, Asthma, and Immunology: **Disease Management of Atopic Dermatitis: An Updated Practice Parameter (2012)**[27]	General considerations • The intensity of management and treatment of atopic dermatitis is dictated by the severity of illness, which relates to the effect of atopic dermatitis on the quality of life on the patient and his or her family. • The management of atopic dermatitis requires multiple therapeutic approaches including antipruritic therapy, skin hydration, topical anti-inflammatory medications, antibacterial measures, and the identification/elimination of exacerbating factors. Skin hydration • Hydration with warm soaking baths for at least 10 minutes followed by the application of a moisturizer is recommended. • Moisturizers should be recommended as first-line therapy. Topical corticosteroids • Topical corticosteroids are an effective treatment option for atopic dermatitis. If atopic dermatitis is not controlled by moisturizers alone, then the clinician should recommend a topical corticosteroid. • Low-potency corticosteroids are recommended for maintenance therapy, whereas intermediate-and high-potency corticosteroids should be used for the treatment of exacerbation and applied to affected areas over short periods of time. • Potent fluorinated corticosteroids should not be used on the face, eyelids, genitalia, and intertriginous areas or in young infants. • Ultrahigh-potency corticosteroids should be used only for very short periods of time (several days) and in nonfacial non-skinfold areas. • The degree of corticosteroid absorption through the skin and the potential for systemic adverse effects are directly dependent on the surface area of the skin involved, thickness of the skin, the use of occlusive dressing, and the potency of the corticosteroid preparation. Topical calcineurin inhibitors • Tacrolimus ointment has been shown to be effective and safe in both adults and children older than two years of age, with most patients experiencing a reduction of pruritus within three days of initiating therapy. • Tacrolimus ointment does not cause atrophy for eczema on the face, eyelid, and skin folds that is unresponsive to low-potency topical steroids. • Once a flare is controlled, tacrolimus ointment twice daily, twice weekly to eczema-prone areas may prevent future flares. • Pimecrolimus cream decreases the number of flares of atopic dermatitis,

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	reduces the need for corticosteroids, and controls pruritus. Tar preparations • There are no randomized studies that have demonstrated the efficacy of tar preparations, despite their widespread use for the treatment of atopic dermatitis. • Newer coal tar products have been developed that are more cosmetically acceptable than older products. • Coal preparations should not be recommended for acutely inflamed skin because this might result in additional skin irritation. Antihistamines • Patients may benefit from the use of oral antihistamines for the relief of pruritus associated with atopic dermatitis. Treatment of atopic dermatitis with topical antihistamines is generally not recommended because of potential cutaneous sensitization. Vitamin D • Patients with atopic dermatitis might benefit from supplementation with vitamin D, particularly if they have a documented low level or low vitamin D intake. Dilute bleach baths • The addition of dilute bleach baths twice weekly may reduce the severity of atopic dermatitis, especially in patients with recurrent skin infections. Microbes • Skin infections with *Staphylococcus aureus* are a recurrent problem in patients with atopic dermatitis, and patients with moderate-to-severe atopic dermatitis have been found to make IgE antibodies against staphylococcal toxins present in their skin. • A short course of an appropriate systemic antibiotic for patients who are clinically infected with *Staphylococcus aureus* should be prescribed. In areas with high levels of methicillin-resistant *Staphylococcus aureus*, treatment with clindamycin, doxycycline, or sulfamethoxazole-trimethoprim may be initiated while awaiting skin culture results. • Atopic dermatitis can be complicated by recurrent viral skin infections, such as herpes simplex, warts, and molluscum contagiosum. Herpes simplex or eczema herpeticum should be diagnosed and promptly treated with systemic antiviral agents. • Fungal infections can complicate atopic dermatitis and might contribute to exacerbations. Systemic Immunomodulating Agents • Immunosuppressive agents such as cyclosporine, interferon gamma, mycophenolate mofetil, azathioprine, and corticosteroids have been shown to provide benefit for certain cases of severe refractory atopic dermatitis, but potential benefits should be weighed against their potentially serious adverse effects. Phototherapy • Ultraviolet therapy can be a useful treatment for recalcitrant atopic dermatitis. Allergen immunotherapy • Select patients with atopic dermatitis with aeroallergen sensitivity may benefit from allergen immunotherapy.
American Academy of	Topical corticosteroids

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Dermatology: **Guidelines of Care for the Management of Atopic Dermatitis (2014)**[28]	• Topical corticosteroids are the mainstay of anti-inflammatory therapy for the management of atopic dermatitis. • They are typically introduced into the treatment regimen after failure of lesions to respond to good skin care and regular use of moisturizers alone. • Comparative trials are limited in duration and scope (i.e., they mainly involve two, and occasionally three, agents), and as a result, there are no data to support one or a few specific agents as being more efficacious than others. • A variety of factors should be considered when choosing a particular topical corticosteroid for the treatment of atopic dermatitis, including patient age, areas of the body to which the medication will be applied, and other patient factors such as degree of xerosis, patient preference, and cost of medication. • Twice-daily application of corticosteroids is generally recommended for the treatment of atopic dermatitis; however, evidence suggests that once-daily application of some corticosteroids may be sufficient. • Proactive, intermittent use of topical corticosteroids as maintenance therapy (one to two times/week) on areas that commonly flare is recommended to help prevent relapses and is more effective than use of emollients alone. • The potential for both topical and systemic side effects, including possible hypothalamic-pituitary-adrenal axis suppression, should be considered, particularly in children with atopic dermatitis in whom corticosteroids are used. • Monitoring by physical examination for cutaneous side effects during long-term, potent steroid use is recommended. • No specific monitoring for systemic side effects is routinely recommended for patients with atopic dermatitis. • Patient fears of side effects associated with the use of topical corticosteroids for atopic dermatitis should be recognized and addressed to improve adherence and avoid undertreatment. <u>Topical calcineurin inhibitors</u> • Topical calcineurin inhibitors are recommended and effective for acute and chronic treatment, along with maintenance, in both adults and children with atopic dermatitis, and are particularly useful in selected clinical situations, including recalcitrance to steroids, use on sensitive areas (e.g., face, anogenital, skin folds), steroid-induced atrophy, and long-term uninterrupted topical steroid use. • Topical calcineurin inhibitors are recommended for use on actively affected areas as a steroid-sparing agent for the treatment of atopic dermatitis. • For patients with atopic dermatitis <2 years of age with mild to severe disease, off-label use of 0.03% tacrolimus or 1% pimecrolimus ointment can be recommended. • Pimecrolimus cream and tacrolimus ointment may cause skin burning and pruritus, especially when applied to acutely inflamed skin. Initial treatment of patients with atopic dermatitis using topical corticosteroids should be considered to minimize topical calcineurin inhibitor application site reactions. Patients with atopic dermatitis should be counseled about the possibility of these reactions. • Proactive, intermittent use of topical calcineurin inhibitor as maintenance therapy (two to three times per week) on areas that commonly flare is recommended to help prevent relapses while reducing the need for topical corticosteroids and is more effective than the use of emollients alone. • The concomitant use of a topical corticosteroid with a topical calcineurin inhibitor may be recommended for the treatment of atopic dermatitis. • No consistent increases in the prevalence of cutaneous viral infections have been seen with continuous or intermittent use of topical calcineurin inhibitor for up to five years; however, physicians should inform their patients of these

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	theoretical cutaneous risks, given the lack of safety data for longer periods of time. • Clinicians should be aware of the black-box warning on the use of topical calcineurin inhibitor for patients with atopic dermatitis and discuss as warranted. • Routine blood monitoring of tacrolimus and pimecrolimus levels in patients with atopic dermatitis who are applying these agents is not recommended at this time. <u>Topical antimicrobials and antiseptics</u> • Except for bleach baths with intranasal mupirocin, no topical antistaphylococcal treatment has been shown to be clinically helpful in patients with atopic dermatitis and is not routinely recommended. In patients with moderate to severe atopic dermatitis and clinical signs of secondary bacterial infection, bleach baths and intranasal mupirocin may be recommended to reduce disease severity. <u>Other topical agents</u> • Topical antihistamines have been tried for the treatment of atopic dermatitis but have demonstrated little utility and are not recommended. • There are not adequate data to make a recommendation regarding the use of coal tar topical agents.
Global Initiative for Asthma (GINA): **Global Strategy for Asthma Management and Prevention (2023)**[29]	Asthma severity is assessed based on the level of treatment required to control symptoms and exacerbations and can change over the course of a few months or years. Severe asthma is defined as asthma that is uncontrolled despite high dose ICS-LABA or that requires high dose ICS-LABA to remain controlled. • Uncontrolled asthma: Poor symptom control and/or frequent exacerbations • Difficult-to-treat asthma: uncontrolled despite prescribing medium or high dose ICS with a second controller (usually LABA) or with a maintenance OCS, or that requires a high dose to maintain good symptom control and reduce risk of exacerbations. • Severe asthma: a subset of difficult-to-treat asthma that is uncontrolled despite adherence with maximal optimized high dose ICS-LABA treatment and management of contributory factors, or that worsens when high dose treatment is decreased. Diagnosis and management pathway for difficult-to-treat and severe asthma (adults and adolescents): • Look for factors contributing to symptoms, exacerbations, and poor quality of life such as poor inhaler technique, suboptimal adherence, or comorbidities. • Optimize management including asthma education, modifying treatment, add-on nonbiologic therapy to medium/high dose ICS (e.g., LABA, LAMA, LTRA), non-pharmacological interventions (e.g., smoking cessation, exercise, weight loss, allergen avoidance, etc.) • If the asthma is still uncontrolled after three to six months, the patient is diagnosed with severe asthma. • Assess the severe asthma phenotype. A patient may have type 2 airway inflammation (blood eosinophils ≥150 cells/µl or FeNO ≥20 ppb or asthma clinically allergen-driven or need for maintenance OCS) ○ If a patient has type 2 inflammation, may consider adherence tests, increase ICS dose for three to six months or add-on type two biologic therapy with anti-IgE, anti-IL5/anti-IL5R or anti-IL4R. No preferred agent mentioned. Suggested initial trial of at least four months. Type 2 comorbidities include things such as nasal

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	polyposis and atopic dermatitis. ○ If a patient is not type 2, may continue to try to optimize management, avoid exposures (tobacco smoke, allergens) or consider add-on treatment with LAMA, LTRA or azithromycin. No biologic options currently available for non-Type 2 severe asthma (guidelines prior to tezepelumab approval).
American Thoracic (ATS) and European Respiratory Society (ERS): Management of Severe Asthma: **An ERS/ATS Guideline (2020 update to 2014 guidelines)**[30]	The ATS-ERS Task Force defines severe asthma for patients ≥ six years of age as asthma requiring high dose inhaled corticosteroids plus a second controller for the previous year or treatment with systemic glucocorticoids for ≥ 50% of the year to prevent it from becoming "uncontrolled" or asthma that remains "uncontrolled" despite receiving this therapy. Uncontrolled asthma is defined as meeting at least one of four criteria: 1) Poor asthma control: ACQ Score ≥1.5 2) Frequent severe asthma exacerbations requiring two or more systemic corticosteroid bursts in the previous year 3) Serious exacerbations resulting in at least one hospitalization, ICU stay or mechanic ventilation in the previous year 4) Limited airflow after appropriate bronchodilator: FEV1 <80% predicted normal Distinguish controlled from uncontrolled severe asthma. Patients meeting any of the four criteria for "uncontrolled asthma" listed above while on high-dose therapy can be identified as having severe asthma. Patients who do not meet the criteria for uncontrolled asthma but worsen on tapered corticosteroids also meet the definition of severe asthma. Treatment of severe asthma: • Suggest using anti-IL5/IL5R therapies in adult patients with severe uncontrolled eosinophilic asthma, with a suggested eosinophil cut point of ≥150 cells/µl. • Suggest using anti-IL4/13 therapy in adult patients with severe eosinophilic asthma (eosinophil cut point not stated) or severe corticosteroid-dependent asthma. • Suggest considering eosinophil cut point of ≥260 cells/µl and FeNO ≥19.5 ppb to identify adults and adolescents with the greatest likelihood of response to anti-IgE therapy. • Suggest using inhaled tiotropium for adolescents and adults with severe uncontrolled asthma despite GINA step 4 to 5 or NAEPP step 5 therapies. • Suggest a trial of chronic macrolide therapy to reduce asthma exacerbations in persistently symptomatic or uncontrolled patients on GINA step 5 or NAEPP step 5 therapies, irrespective of asthma phenotype.
National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group: **Focused Updates to the Asthma Management Guidelines. National Heart Lung and Blood Institute (2020)**[31]	Management of persistent asthma in Individuals 5 to 11 Years Preferred • Step 1- PRN SABA • Step 2- Daily low-dose ICS and PRN SABA • Step 3- Daily and PRN combination low-dose ICS-formoterol (Consider the addition of omalizumab) • Step 4- Daily and PRN combination medium-dose ICS-formoterol (Consider the addition of omalizumab) • Step 5 Daily high-dose ICS-LABA and PRN SABA (Omalizumab can be considered) • Step 6 – Daily high dose ICS-LABA + oral systemic corticosteroid and PRN SABA (Omalizumab can be considered) Management of Persistent Asthma in Individuals Ages 12+ Years Preferred

Clinical Guideline	Recommendation(s)
	• Step 1- PRN SABA • Step 2- Daily low-dose ICS and PRN SABA or PRN concomitant ICS and SABA • Step 3- Daily and PRN combination low-dose ICS-formoterol • Step 4- Daily and PRN combination medium-dose ICS-formoterol • Step 5- Daily medium-high dose ICS-LABA plus LAMA and PRN SABA (Consider adding asthma biologics [e.g., anti-IgE, anti-IL5, anti-IL5R, anti-IL4/IL13) • Step 6- Daily high-dose ICS-LABA plus oral systemic corticosteroids plus PRN SABA (Consider adding asthma biologics [e.g., anti-IgE, anti-IL5, anti-IL5R, anti-IL4/IL13)
The Joint Task Force on Practice Parameters: **GRADE guidelines for the medical management of chronic rhinosinusitis with nasal polyposis (2023)**[32]	Recommendation 1: In people with CRSwNP, the guideline panel suggests INCS rather than no INCS (conditional recommendation based on low certainty of evidence). Recommendation 2: In people with CRSwNP, the guideline panel suggests biologics rather than no biologics (conditional recommendation based on moderate certainty of evidence). • For patients who have a symptom for which the improvement was considered to be important while receiving treatments other than biologics (i.e., INCS, surgery, or ATAD), not using biologics may be preferred. • For patients using INCS for at least 4 weeks and who continue to have high disease burden, biologics may be preferred over other medical treatment choices. • For patients who have higher disease severity at presentation, biologics may be preferred over other medical treatment choices. • There is variability in efficacy among the biologics and this may influence the overall choice. Dupilumab and omalizumab are the most beneficial for most patient-important outcomes when comparing with other biologics based on results from the Oykhman et al9 NMA linked to this guideline. • Patients who value not having the burden of payment and insurance approvals may be less likely to choose biologics. • Patients who want to avoid the inconvenience of trying potentially less effective medical therapies may prefer biologics. • In AERD specifically, biologics may be preferred over ATAD for patients who have increased risk of harms associated with daily aspirin therapy, in patients who value the most efficacious therapies, and/or in patients who wish to avoid a strict daily oral medication regimen and its associated initial desensitization procedure. • Patients with comorbid diseases that led to a dual indication for biologic treatment (e.g., asthma) may be a reason to choose biologics in general and even specific biologics.
AGA Institute and the Joint Task Force on Allergy-Immunology: **Practice Parameters Clinical Guidelines for the Management of Eosinophilic Esophagitis (2020)**[33]	• In patients with symptomatic esophageal eosinophilia, the AGA/JTF suggests using proton pump inhibition over no treatment (Conditional recommendation, very low-quality evidence) • In patients with EoE, the AGA/JTF recommends topical glucocorticoids over no treatment (strong recommendations, moderate quality evidence) • In patients with EoE, the AGA/JTF suggests topical glucocorticoids rather than oral glucocorticoids (conditional recommendation, moderate quality evidence) • In patients with EoE, the AGA/JTF suggests allergy testing-based elimination diet over no treatment (conditional recommendation, very low-quality evidence) • In adult patients with dysphagia from a stricture associated with eosinophilic esophagitis, the AGA/JTF suggests endoscopic dilation over no dilation (conditional recommendation, very low-quality evidence)

Clinical Guideline	Recommendation(s)
	• In patients with EoE, the AGA/JTF recommends using anti-interleukin-5 therapy only in the context of a clinical trial (No recommendation; knowledge gap) • In patients with EoE, the AGA/JTF recommends using anti-IL-13 or anti-IL-4 receptor-alpha therapy for EoE only in the context of a clinical trial (no recommendation; knowledge gap) • In patients with EoE the AGA/JTF suggests against the use of anti-IgE therapy for EoE (Conditional recommendations; very low-quality evidence) • In patients with EoE, the AGA/JTF recommends topical steroids over no treatment (strong recommendation, moderate quality evidence) • In patients with EoE, the AGA/JTF suggest using montelukast, cromolyn sodium, immunomodulators and anti-TNF only in the context of a clinical trial (No recommendation; knowledge gap)

III.Indications

The Food and Drug Administration (FDA)-approved indications for the skin and mucus membrane immunomodulators are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Skin and Mucus Membrane Immunomodulators[1-13]

Indications	Bimekizumab	Brodalumab	Deucravacitinib	Dupilumab	Guselkumab	Ixekizumab	Risankizumab	Spesolimab	Tildrakizumab	Tralokinumab	Ustekinumab
Ankylosing Spondylitis						✔					
Asthma*				✔							
Atopic dermatitis				✔						✔	
Crohn's Disease							✔				✔
CRwNP				✔							
Eosinophilic esophagitis				✔							
Non-radiographic axSpA						✔					
Plaque psoriasis	✔	✔	✔		✔	✔	✔		✔		✔
Prurigo nodularis				✔							
Psoriatic arthritis					✔	✔	✔				✔
Pustular psoriasis								✔			
Ulcerative Colitis											✔

CRwNP=Chronic rhinosinusitis with nasal polyposis, axSpA=axial spondyloarthritis,
*moderate to severe eosinophilic or oral glucocorticoid dependent.

IV.Pharmacokinetics

The pharmacokinetic parameters of the skin and mucus membrane immunomodulators are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Skin and Mucus Membrane Immunomodulators[13]

Generic Name(s)	Bioavailability (%)	Time to Peak Concentration	Half-Life
Bimekizumab	70	Not reported	23 days

Brodalumab	55	3 days	Not reported
Deucravacitinib	99	2 to 3 hours	10 hours
Dupilumab	60 to 64	1 week	Not reported
Guselkumab	49	5.5 days	15 to 18 days
Ixekizumab	60 to 81	4 days	13 days
Risankizumab	74 to 89	3 to 14 days	21 to 28 days
Spesolimab	Not reported	Not reported	25.5 days
Tildrakizumab	73 to 80	6 days	23 days
Tralokinumab	76	5 to 8 days	3 weeks
Ustekinumab	Not reported	7 to 13.5 days	14.9 to 45.6 days

V.Drug Interactions

Major drug interactions with the skin and mucus membrane immunomodulators are listed in Table 5.

Table 5. Major Drug Interactions with the Skin and Mucus Membrane Immunomodulators[13]

Generic Name(s)	Interaction	Mechanism
Bimekizumab, brodalumab, deucravacitinib, dupilumab, guselkumab, ixekizumab, risankizumab, spesolimab, tildrakizumab, tralokinumab, ustekinumab	Live vaccines	Concurrent use of may result in reduced effectiveness of live vaccines.
Bimekizumab, brodalumab, deucravacitinib, dupilumab, guselkumab, ixekizumab, risankizumab, spesolimab, tildrakizumab, tralokinumab, ustekinumab	Other biologic immunomodulators	Concurrent use may increase the risk of infections.
Bimekizumab, ustekinumab	Cyclosporine	Concurrent use of may result in altered cyclosporine exposure.
Bimekizumab, ustekinumab	Warfarin	Concurrent use of may result in altered warfarin exposure.

VI.Adverse Drug Events

The most common adverse drug events reported with the skin and mucus membrane immunomodulators are listed in Table 6. The boxed warnings are listed in Table 7.

Table 6. Adverse Drug Events (%) Reported with the Skin and Mucus Membrane Immunomodulators[1-13]

Adverse Event	Bimekizumab	Brodalumab	Deucravacitinib	Dupilumab	Guselkumab	Ixekizumab	Risankizumab	Spesolimab	Tildrakizumab	Tralokinumab	Ustekinumab
Gastrointestinal											
Abdominal pain	-	-	-	-	-	-	6 to 9	-	-	-	7
Diarrhea	-	2	-	3	1.6	-	-	-	2	-	2 to 4
Gastritis	-	-	-	2	-	-	-	-	-	-	-
Gastroenteritis	2	-	-	-	1.3	-	-	-	-	-	-
Nausea	-	2	-	-	-	2	-	9	-	-	3
Vomiting	-	-	-	-	-	-	-	9	-	-	4
Laboratory Tests											
Creatinine phosphokinase increased	-	-	2.7	-	-	-	-	-	-	-	-
Eosinophilia	-	-	-	<3	-	-	-	-	-	1	-
Neutropenia	-	1	-	-	-	11	-	-	-	-	-
Thrombocytopenia	-	-	-	-	-	3	-	-	-	-	-
Respiratory											
Bronchitis	-	-	-	-	-	-	-	-	-	-	5
Dyspnea	-	-	-	-	-	-	-	3	-	-	-
Nasopharyngitis	-	-	-	5	-	-	-	-	-	-	7 to 24
Sinusitis	-	-	-	-	-	-	-	-	-	-	3 to 4
Upper respiratory infection	-	-	19.2	18	14	14	11 to 13	3	14	24	4 to 5
Skin											
Acne	1	-	1.4	-	-	-	-	-	-	-	1
Cellulitis	-	-	-	-	-	-	-	3	-	-	-
Folliculitis	1	-	1.7	-	-	-	-	-	-	-	-
Infusion site hematoma and bruising	-	-	-	-	-	-	-	6	-	-	-
Pruritus	-	-	-	-	-	-	-	6	-	-	1 to 2
Urticaria	-	-	-	-	-	≤2	-	3	-	-	-
Other											
Antibody development	45	3	-	1 to 16	6 to 9	5 to 22	3 to 24	-	7	-	3 to 12
Arthralgia	-	4.7	-	2 to 3	2.7	-	5 to 9	-	-	-	3
Back pain	-	-	-	-	-	-	4	-	-	-	1 to 2
Bacteremia	-	-	-	-	-	-	-	3	-	-	-

Adverse Event	Bimekizumab	Brodalumab	Deucravacitinib	Dupilumab	Guselkumab	Ixekizumab	Risankizumab	Spesolimab	Tildrakizumab	Tralokinumab	Ustekinumab
Bactiuria	-	-	-	-	-	-	-	3	-	-	-
Cellulitis	-	-	-	-	-	-	-	3	-	-	-
Conjunctivitis	-	-	-	0 to 10	-	3	-	-	-	6 to 9	-
Depression	-	-	-	-	-	-	-	-	-	-	1
Dizziness	-	-	-	3	-	-	-	-	-	-	1 to 2
Eye edema	-	-	-	-	-	-	-	3	-	-	-
Fatigue	1	3	-	-	-	-	3	9	-	-	3
Fever	-	-	-	-	-	-	5	-	-	-	-
Headache	3	4.3	-	-	4.6	-	3.5	9	-	-	5 to 10
Herpes simplex	-	-	2	-	1.1	-	-	3	-	-	-
Infection	36	25	29	-	23	Up to 57	3 to 37	14	23	-	27
Influenza	-	1.3	-	-	-	-	-	-	-	-	6
Injection site pain	-	-	-	-	-	17	1.5	-	-	-	-
Injection site reaction	3	1.5	-	6 to 38	4.5	-	2 to 6	-	3	7	1 to 2
Insomnia	-	-	-	1	-	-	-	-	-	-	-
Malignant neoplasm	-	-	-	-	-	-	-	-	-	-	2
Mouth ulcer	-	-	1.9	-	-	-	-	-	-	-	-
Muscle Pain	-	1.7	-	-	-	-	-	-	-	-	1
Myalgia	-	-	-	3	-	-	-	-	-	-	-
Oropharyngeal pain	-	2.1	-	-	-	-	-	-	-	-	-
Pharyngo-laryngeal pain	-	-	-	-	-	-	-	-	-	-	1 to 2
Suicidal ideation	2	-	-	-	-	-	-	-	-	-	-
Tinia infections	3	1	-	-	1.1	2	1.1	-	-	-	-
Urinary tract infection	-	-	-	-	-	-	4	6	-	-	4

-Event not reported or incidence <1%.

Table 7. Boxed Warning for Brodalumab[12]

WARNING
Suicidal ideation and behavior: Suicidal ideation and behavior, including completed suicides, have occurred. Prior to prescribing, weigh potential risks and benefits in patients with a history of depression and/or suicidal ideation or behavior. Patients with new or worsening suicidal thoughts and behavior should be referred to a mental health professional, as appropriate. Advise patients and caregivers to seek medical attention for manifestations of suicidal ideation or behavior, new onset or worsening depression, anxiety, or other mood changes. Brodalumab is available only through a Risk Evaluation and Mitigation Strategy (REMS) Program.

VII. Dosing and Administration

The usual dosing regimens for the skin and mucus membrane immunomodulators are listed in Table 8.

Table 8. Usual Dosing Regimens for the Skin and Mucus Membrane Immunomodulators[1-13]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Bimekizumab	Moderate to severe plaque psoriasis: Injection: 320 mg (given as 2 subcutaneous injections of 160 mg each) at Weeks 0, 4, 8, 12, and 16, then every 8 weeks thereafter. For patients weighing ≥ 120 kg, consider a dosage of 320 mg every 4 weeks after Week 16	Safety and efficacy in the pediatric population have not been established.	160 mg/mL in a single-dose prefilled syringe or single-dose prefilled autoinjector
Brodalumab	Moderate to severe plaque psoriasis: Prefilled syringe: initial, 210 mg SC at weeks 0, 1, and 2; maintenance, 210 mg every two weeks	Safety and efficacy in the pediatric population have not been established.	Prefilled syringe: 210 mg/1.5 mL
Deucravacitinib	Moderate to severe plaque psoriasis: Tablet: 6 mg by mouth once daily	Safety and efficacy in the pediatric population have not been established.	Tablet: 6 mg
Dupilumab	Atopic dermatitis (moderate-severe): Injection: 600 mg (two 300 mg injections) subcutaneous load followed by 300 mg every two weeks CRSwNP Injection: 300 mg subcutaneously every two weeks Moderate-to-severe eosinophilic asthma or OCS-dependent asthma: Injection: 400 mg (two 200 mg injections) followed by 200 mg every two weeks OR 600 mg (two 300 mg injections) followed by 300 mg every two weeks (For individuals with oral corticosteroid-dependent asthma or co-morbid moderate-to-severe atopic dermatitis or adults with comorbid chronic rhinosinusitis with nasal	Atopic dermatitis (moderate-severe): *Patients 6 months to 5 years of age*: 5 to < 15 kg: 200 mg every four weeks 15 to < 30 kg: 300 mg every four weeks *Patients 6 years to 17 years of age*: 15 to < 30 kg: 600 mg subcutaneous load followed by 300 mg every four weeks 30 to < 60 kg: 400 mg subcutaneous load followed by 200 mg every two weeks Moderate-to-severe eosinophilic asthma or OCS-dependent asthma: *Patients ≥12 years of age*: 400 mg (two 200 mg injections) followed by 200 mg every two	300 mg/2 mL prefilled syringe 300 mg/2 mL prefilled pen 200 mg/1.14 mL prefilled syringe 200 mg/1.14 mL prefilled pen 100 mg/0.67 mL prefilled syringe

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	polyposis for which dupilumab is indicated, start with an initial dose of 600 mg followed by 300 mg every two weeks) Eosinophilic esophagitis: Injection: 15 to < 30 kg: 200 mg every other week; 30 to <40 kg: 300 mg every other week; ≥40 kg: 300 mg every week Prurigo Nodularis: Injection: Loading dose of 600 mg (two 300 mg injections) subcutaneously followed by 300 mg every other week	weeks OR 600 mg (two 300 mg injections) followed by 300 mg every two weeks (For individuals with oral corticosteroid-dependent asthma or co-morbid moderate-to-severe atopic dermatitis or adults with comorbid chronic rhinosinusitis with nasal polyposis for which dupilumab is indicated, start with an initial dose of 600 mg followed by 300 mg every two weeks) *Patients 6 to 11 years of age*: 15 to < 30 kg: 100 mg every two weeks or 300 mg every four weeks Members 6 to 11 years of age and ≥ 30 kg: 200 mg every two weeks *Patients 6 to 11 years of age with asthma and co-morbid moderate-to-severe atopic dermatitis*: loading dose can be given (600 mg for those 15 to < 30 kg; 400 mg for those 30 to < 60 kg; 600 mg for those ≥ 60 kg) Eosinophilic esophagitis: *Patients aged one year and older, weighing at least 15 kg*: 15 to < 30 kg: 200 mg every other week 30 to <40 kg: 300 mg every other week ≥40 kg: 300 mg every week	
Guselkumab	Plaque psoriasis, psoriatic arthritis: Injection: initial, 100 mg SC at weeks 0 and 4; maintenance, 100 mg SC every 8 weeks	Safety and efficacy in the pediatric population have not been established.	One-Press patient-controlled injector: 100 mg/mL Prefilled syringe: 100 mg/mL
Ixekizumab	Moderate to severe plaque psoriasis: Injection: initial, 160 mg SC at week 0; 80 mg at weeks 2, 4, 6, 8, 10, 12; maintenance, 80 mg every 4 weeks Psoriatic arthritis, ankylosing spondylitis:	Moderate to severe plaque psoriasis in patients 6 years of age and older: Injection: weight >50 kg, initial, 160 mg SC at week 0; maintenance, 80 mg SC every 4 weeks; weight 25 to 50 kg, initial	Autoinjector: 80 mg/mL Prefilled syringe: 80 mg/mL

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	Injection: initial, 160 mg SC at week 0; maintenance, 80 mg every 4 weeks Non-radiographic axial spondyloarthritis: Injection: 80 mg every 4 weeks	80 mg SC at week 0; maintenance, 40 mg SC every 4 weeks; weight < 25 kg, initial 40 mg SC at week 0; maintenance, 20 mg SC every 4 weeks	
Risankizumab	Crohn's disease: Injection: initial, 600 mg IV at weeks 0, 4, and 8; maintenance, 180 mg or 360 mg SC at week 12 and every 8 weeks thereafter Plaque psoriasis and Psoriatic arthritis: Injection: initial, 150 mg SC at weeks 0 and 4, maintenance, 150 mg SC every 12 weeks	Safety and efficacy in the pediatric population have not been established.	Pen: 150 mg/mL Prefilled syringe: 75 mg/0.83 mL 90 mg/mL 150 mg/mL Prefilled cartridge: 180 mg/1.2 mL 360 mg/2.4 mL Vial: 600 mg/10mL
Spesolimab	Generalized pustular psoriasis flares: Vial: 900 mg IV once; If symptoms persist, an additional 900 mg IV dose may be administered one week after the initial dose	Safety and efficacy in the pediatric population have not been established.	Vial: 450 mg/7.5 mL
Tildrakizumab	Moderate to severe plaque psoriasis: Prefilled syringe: initial, 100 mg SC at weeks 0 and 4; maintenance, 100 mg SC every 12 weeks thereafter	Safety and efficacy in the pediatric population have not been established.	Prefilled syringe: 100 mg/mL
Tralokinumab	Moderate-to-severe atopic dermatitis: Injection: Initial, 600 mg; maintenance, 300 mg every other week (a dosage of 300 mg every 4 weeks may be considered for adult patients below 100 kg who achieve clear or almost clear skin after 16 weeks of treatment)	Moderate-to-severe atopic dermatitis in patients aged 12 years and older: Injection: Initial, 300 mg; maintenance, 150 mg every other week	Prefilled syringe: 150 mg/mL
Ustekinumab	Crohn's disease and ulcerative colitis: Injection: initial, 260 to 520 mg (weight-based dosing) IV, maintenance; 90 mg SC every 8 weeks Plaque psoriasis and psoriatic arthritis: Injection: for weight ≤100 kg, initial, 45 mg SC at weeks 0 and 4; maintenance, 45 mg SC every 12 weeks	Plaque psoriasis and psoriatic arthritis in patients 6 years of age or older: Injection: for weight <60 kg, initial, 0.75 mg/kg SC at weeks 0 and 4; maintenance, 0.75 mg/kg mg SC every 12 weeks for weight 60 to 100 kg, initial, 45 mg SC at weeks 0 and 4; maintenance, 45 mg SC every 12 weeks for weight >100 kg, initial, 90 mg SC at weeks 0 and 4;	Prefilled syringe: 45 mg/0.5 mL 90 mg/mL Vial: 45 mg/0.5 mL 130 mg/26 mL

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	for weight >100 kg, initial, 90 mg SC at weeks 0 and 4; maintenance, 90 mg SC every 12 weeks	maintenance, 90 mg SC every 12 weeks	

IV=intravenously, SC=subcutaneously
CRSwNP=chronic rhinosinusitis with nasal polyposis, JIA=juvenile Idiopathic Arthritis, NOMID=Neonatal-Onset Multisystem Inflammatory Disease

VIII.Effectiveness

Clinical studies evaluating the safety and efficacy of the skin and mucus membrane immunomodulators are summarized in Table 9.

Table 9. Comparative Clinical Trials with the Skin and Mucus Membrane Immunomodulators

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Asthma				
Castro et al.[34] (2018) Liberty Asthma QUEST Dupilumab 200 mg SC every two weeks (loading dose, 400mg) vs Dupilumab 300 mg SC every two weeks (loading dose, 600mg) vs placebo All patients also continued stable dosages of background asthma controller therapies. Use of short-acting β_2-agonists was allowed as rescue therapy for worsening asthma.	DB, PC, PG, RCT Patients ≥ 12 years of age with physician-diagnosed persistent asthma for ≥ 12 months according to the GINA 2014 guidelines if they had current treatment with a medium-to-high dose ICS plus up to two additional controllers; a FEV_1 before bronchodilator use of ≤80% of the predicted normal value (or ≤ 90% of the predicted normal value in those 12 to 17 years of age); FEV_1 reversibility of at least 12% and 200 mL; a (ACQ-5 of ≥ 1.5 (on a scale from 0 [no impairment] to 6 [maximum impairment]; the minimal clinically important difference is 0.5); and a worsening of asthma in the previous year that led	N=1,902 52 weeks	Primary: Annualized rate of severe exacerbation events (number of severe exacerbations per patient-year) during the 52-week intervention period and the absolute change from baseline in the FEV_1 before bronchodilator use at week 12 in the overall trial population Secondary Annualized rate of severe exacerbation events (number of severe exacerbations per patient-year) during the 52-week intervention period and the absolute change from baseline in the FEV_1 before bronchodilator use at week 12 for those with a blood eosinophil count of	Primary: Results highlighted that the annualized rate of severe asthma exacerbations was 0.46 (95% CI, 0.39 to 0.53) among patients assigned to 200 mg of dupilumab every two weeks and 0.87 (95% CI, 0.72 to 1.05) among those assigned to a matched placebo, for a 47.7% lower rate with dupilumab than with placebo (P<0.001). The rate was 0.52 (95% CI, 0.45 to 0.61) among patients assigned to 300 mg of dupilumab every two weeks versus 0.97 (95% CI, 0.81 to 1.16) among those assigned to matched placebo (46.0% lower rate with dupilumab than with placebo, P<0.001). In the overall trial population, the change from baseline in the FEV_1 before bronchodilator use at week 12 was 0.32 L with lower-dose dupilumab vs 0.18 L with matched placebo (P<0.001). The change from baseline in the FEV_1 before bronchodilator use at week 12 for the higher-dose dupilumab was 0.34 vs 0.21 with matched placebo (P<0.001). Secondary: Among patients with a blood eosinophil count ≥ 300 cells/μL, the annualized rate of severe asthma exacerbations was 0.37 (95% CI, 0.29 to 0.48) among those receiving lower-dose dupilumab and 1.08 (95% CI, 0.85 to 1.38) among those receiving a matched placebo (65.8% lower rate with dupilumab than with placebo; 95% CI, 52.0 to 75.6) and 0.40 (95% CI, 0.32 to 0.51) with higher-dose dupilumab versus 1.24 (95% CI, 0.97 to 1.57) with placebo (67.4% lower rate with dupilumab than placebo, P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	to hospitalization, emergency medical care, or treatment with systemic glucocorticoids for ≥3 days		300 or more per cubic millimeter	In subjects with baseline blood eosinophil count < 150 cells/μL, similar severe exacerbation rates were observed between dupilumab and placebo. At week 12, the FEV_1 had increased by 0.32 L in the overall trial population assigned to the lower dose of dupilumab (difference vs placebo, 0.14 L; P<0.001); similar results were seen with the higher dose.
Rabe et al.[35] (2018) Dupilumab 300 mg SC every two weeks (loading dose, 600 mg) vs placebo	DB, PC, RCT Patients ≥12 years old who had physician-diagnosed asthma for ≥ 1 year according to the GINA 2014 guidelines and who had been receiving treatment with regular systemic glucocorticoids in the previous 6 months (5 to 35 mg per day of prednisone or prednisolone or equivalent). During the 4 weeks before screening, treatment had to also include a high-dose ICS in combination with up to two controllers for at least 3 months. FEV_1 before bronchodilator use of ≤80% of the predicted normal value (or ≤90% of the predicted normal value	N=210 24 weeks	Primary: Percentage reduction in glucocorticoid dose at week 24 Secondary: Proportion of patients at week 24 with a reduction of at least 50% in the glucocorticoid dose and the proportion of patients with a reduction to a glucocorticoid dose of less than 5 mg per day.	Primary: In the intention-to-treat population, the least-squares mean (±SE) percentage change in the oral glucocorticoid dose from baseline to week 24, while asthma control was maintained, was −70.1 ± 4.9% in the dupilumab group, as compared with −41.9 ± 4.6% in the placebo group (P<0.001). Secondary: The proportion of patients with a glucocorticoid dose reduction of at least 50% was 80% in the dupilumab group vs 50% in the placebo group. The proportion of patients with a dose reduction to less than 5 mg per day was 69% in the dupilumab group vs 33% in the placebo group. Lastly, 48% of patients in the dupilumab group completely discontinued oral glucocorticoids compared to 25% in the placebo group. The observed median change in the oral glucocorticoid dose from baseline to week 24 was −100% (interquartile range, −100 to −62.5) in the dupilumab group, as compared with −50% (interquartile range, −100 to 0) in the placebo group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	in adolescents), FEV_1 reversibility of at least 12% and 200 ml, or airway hyperresponsiveness documented in the 12 months before screening visit 1. There was no minimum requirement regarding baseline blood or sputum eosinophil count or any other type 2 biomarkers			
Wenzel et al.[36] (2016) Dupilumab 200 mg every four weeks vs Dupilumab 300 mg every four weeks vs Dupilumab 200 mg every two weeks vs Dupilumab 300 mg every two weeks vs	DB, PC, PG, RCT Adults (aged ≥18 years) with an asthma diagnosis for ≥12 months based on the Global Initiative for Asthma 2009 Guidelines, receiving treatment with medium-to-high-dose ICS plus a LABA with a stable dose for at least 1 month before screening; a pre-bronchodilator FEV_1 of 40 to 80% predicted at screening and at baseline; an ACQ-5 score of ≥1.5 at screening and at baseline; and reversibility of at least	N=769 24 weeks	Primary: Change from baseline at week 12 in FEV_1 in patients with baseline blood eosinophil counts of ≥ 300 eosinophils per µL assessed in the intention-to-treat population Secondary: Secondary endpoints: Percentage change from baseline in FEV_1; annualized severe asthma exacerbation rate during treatment and overall study periods; time to severe exacerbation events during treatment and	Primary: In the subgroup with at least 300 eosinophils per µL, the greatest increases (200 mg every two weeks, P=0.0008; 300 mg every two weeks, P=0.0063) in FEV_1 compared with placebo were observed at week 12 with doses every two weeks in the 300 mg group (mean change 0.39 L [SE 0.05]; mean difference 0.21 [95% CI, 0.06 to 0.36; P=0.0063]) and in the 200 mg group (mean change 0.43 L [SE 0.05]; mean difference 0.26 [0.11 to 0.40; P=0.0008]) compared with placebo (0.18 L [SE 0.05]). Similar increases were observed in the overall population and in the fewer than 300 eosinophils per µL subgroup (overall population: 200 mg every 2 weeks, P<0.0001; 300 mg every 2 weeks, P<0.0001; <300 eosinophils per µL: 200 mg every 2 weeks, P=0.0034; 300 mg every 2 weeks, P=0.0086), and were maintained to week 24. Likewise, dupilumab every 2 weeks produced the greatest reductions in annualized rates of exacerbation in the overall population (70 to 70.5%), the subgroup with at least 300 eosinophils per µL (71.2 to 80.7%), and the subgroup with fewer than 300 eosinophils per µL (59.9 to 67.6%). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	12% and 200 mL in FEV_1 after 200 to 400 µg of salbutamol at screening. Patients were also required for study inclusion to have had any of the following within 1 year before screening: at least one systemic (oral or parenteral) corticosteroid burst therapy, or a hospital admission or an emergency or urgent medical care visit that required treatment with systemic steroids for worsening asthma		overall study periods; and change from baseline at week 12 and week 24 in morning and evening asthma symptom scores	During the 24-week treatment period, dupilumab every 2 weeks significantly reduced the annualized rates of severe asthma exacerbations compared with placebo. In the overall population, significant reductions in annualized severe asthma exacerbations were observed in patients receiving doses every 2 weeks. In the overall population and in both subgroups, dupilumab every 2 weeks significantly delayed time to first severe exacerbation versus placebo (overall population: 200 mg every 2 weeks, P<0.0001; 300 mg every 2 weeks, P=0.0002; ≥300 eosinophils per µL: 200 mg every 2 weeks, P=0.0008; 300 mg every 2 weeks, P=0.0048; < 300 eosinophils per µL; 200 mg every 2 weeks, P=0.0092; 300 mg every 2 weeks, P=0.0130. In the overall population and in the subgroup with eosinophil counts of at least 300 eosinophils per µL, improvements in ACQ-5 total scores at week 24 relative to baseline were significantly greater in patients receiving dupilumab every 2 weeks than in those receiving placebo. In the overall population, the global AQLQ scores at week 24 relative to baseline were significantly higher in patients receiving dupilumab dose regimens every 2 and 4 weeks than in those receiving placebo, except for those receiving 200 mg dupilumab every 4 weeks. In the subgroup with counts of at least 300 eosinophils per µL, the global AQLQ scores relative to baseline were significantly higher across all dose regimens of dupilumab compared with placebo. In the overall population and in the subgroup with counts of at least 300 eosinophils per µL, morning and evening asthma symptom scores at week 24 relative to baseline significantly improved for both doses given every 2 weeks and for 300 mg dupilumab every 4 weeks. For the subgroup with fewer than 300 eosinophils per µL, morning symptom scores were significantly improved for both

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				doses given every 2 weeks. The most common adverse events with dupilumab compared with placebo were upper respiratory tract infections and injection-site reactions.
Atopic Dermatitis				
Bieber et al.[37] (2021) JADE COMPARE Abrocitinib 100 mg orally once daily vs abrocitinib 200 mg orally once daily vs dupilumab 300 mg subcutaneously every other week (after a loading dose of 600 mg) vs placebo	DB, MC, PC, RCT Adults with moderate-to-severe atopic dermatitis who were receiving background topical therapy	N=838 16 weeks	Primary: IGA response (defined as a score of 0 or 1 on the IGA, with an improvement of ≥2 points from baseline) and an EASI-75 response (defined as ≥75% improvement from baseline in the score on the EASI) at week 12 Secondary: Itch response (defined as ≥4-point improvement from baseline in the score on the PP-NRS) at week two and IGA and EASI-75 responses at week 16	Primary: An IGA response at week 12 was observed in 48.4% of patients in the 200 mg abrocitinib group, 36.6% in the 100 mg abrocitinib group, 36.5% in the dupilumab group, and 14.0% in the placebo group (P<0.001 for both abrocitinib doses vs. placebo); an EASI-75 response at week 12 was observed in 70.3%, 58.7%, 58.1%, and 27.1%, respectively (P<0.001 for both abrocitinib doses vs. placebo). Secondary: The weighted difference in the percentage of patients who had an itch response at week two between the 200 mg abrocitinib group and the placebo group was 34.9 percentage points (95% CI, 26.0 to 43.7) and that between the 100 mg abrocitinib group and the placebo group was 17.9 percentage points (95% CI, 9.5 to 26.3) (P<0.001 for both comparisons). The weighted difference in the percentage of patients who had an itch response at week two between the 200 mg abrocitinib group and the dupilumab group was 22.1 percentage points favoring this dose of abrocitinib (95% CI, 13.5 to 30.7; P<0.001). The weighted difference between the 100 mg abrocitinib group and the dupilumab group was 5.2 percentage points (95% CI, –2.9 to 13.4; P=0.20), indicating no significant difference between the trial groups for this dose of abrocitinib. The weighted difference in the percentage of patients who had an IGA response at week 16 between the 200 mg abrocitinib group and the placebo group was 35.0 percentage points (95% CI, 26.3 to 43.7) and that between the 100 mg abrocitinib group and the placebo group was 22.1 percentage points (95% CI, 13.7 to 30.5) (P<0.001 for both comparisons). The weighted difference in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				percentage of patients who had an IGA response at week 16 between the 200 mg abrocitinib group and the dupilumab group was 9.4 percentage points (95% CI, 0.4 to 18.5), and the difference between the 100 mg abrocitinib group and the dupilumab group was –3.5 percentage points (95% CI, –12.2 to 5.2). The weighted difference in the percentage of patients who had an EASI-75 response at week 16 between the 200 mg abrocitinib group and the placebo group was 40.4 percentage points (95% CI, 30.4 to 50.4; P<0.001) and that between the 100 mg abrocitinib group and the placebo group was 29.7 percentage points (95% CI, 19.5 to 39.9; P<0.001). The weighted difference in the percentage of patients who had an EASI-75 response at week 16 between the 200 mg abrocitinib group and the dupilumab group was 5.5 percentage points (95% CI, –3.1 to 14.1), and the difference between the 100 mg group and the dupilumab group was –5.1 percentage points (95% CI, –13.9 to 3.7). Therefore, both doses of abrocitinib were not significantly different from dupilumab with respect to an EASI-75 response at week 16.
Reich et al.[38] (2022) JADE DARE Abrocitinib 200 mg by mouth per day vs dupilumab 300 mg subcutaneous every 2 weeks	AC, DB, MC, RCT Adults with moderate-to-severe atopic dermatitis who required systemic therapy or had inadequate response to topical medications	N=727 26 weeks	Primary: Response based on achieving a 4 point or higher improvement in Peak Pruritus Numerical Rating Scale (PP-NRS4) at week 2 and a 90% or better improvement in Eczema Area and Severity Index (EASI-90) at week 4 Secondary: Response based on achieving EASI-90 at	Primary: The proportion of patients who reached the primary endpoint of PP-NRS4 at week two was higher in the abrocitinib group than in the dupilumab group (172 [48%] of 357; 95% CI, 43.0 to 53.4 vs 93 [26%] of 364; 21.1 to 30.0). The difference between the abrocitinib and dupilumab groups was 22.6% (95% CI, 15.8 to 29.5; P<0.0001). The proportion of patients who reached the other primary endpoint, EASI-90 at week four, was also higher in the abrocitinib group than in the dupilumab group (101 [29%] of 354; 95% CI, 23.8 to 33.2 vs 53 [15%] of 364; 10.9% to 18.2%), and the between-group difference was 14.1% (8.2 to 20.0; P<0.0001). Secondary: In addition, 194 (54%) of 357 patients (49.2 to 59.5) treated with abrocitinib reached the key secondary endpoint of EASI-90 at

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			week 16; safety	week 16, compared with 151 (42%) of 360 patients (36.8 to 47.0) in the dupilumab group. This resulted in a between-group difference of 12.5% (5.3 to 19.7), which achieved both non-inferiority (lower bound of the 95% CI interval higher than −10%) and superiority (P=0.0008). The 727 patients who made up the safety population had 1417 adverse events (817 with abrocitinib and 600 with dupilumab) during the 26-week treatment period and the 28-day safety follow-up after the last dose of study medication. More patients who received abrocitinib than dupilumab had adverse events (268 [74%] of 362 vs 239 [65%] of 365); the proportions of patients who had adverse events that were serious, severe, or led to study discontinuation were similar between the two treatment groups.
Simpson et al.[39] (2017) SOLO 1 Dupilumab 300 mg SQ every week vs dupilumab 300 mg SQ every other week vs placebo	DB, MC, PC, RCT Patients ≥ 18 years of age with moderate-to-severe AD (IGA 3 or 4), inadequately controlled by topical treatment or medically inadvisable with AD ≥ three years	N= 671 16 weeks	Primary: proportion of patients with IGA (0,1) Secondary: EASI75 response, EASI50 response, reduction in itch by ≥4 points	Primary: IGA (0,1) responses at week 16 were achieved by a significantly higher proportion of the dupilumab-treated patients. The proportion of patients with IGA (0,1) response was 38% for the dupilumab 300 mg every other week and 37% for the dupilumab 300 mg every week compared to 10% for placebo (P<0.001). Secondary: There was a significantly greater improvement in secondary endpoints with dupilumab compared to placebo. A greater proportion of dupilumab-treated patients had EASI75 response compared to placebo at 52% and 51% to 15% (P<0.001). The percentage of patients with EASI50 was 61% and 69% for the dupilumab-treated patients compared to 25% for placebo (P<0.001). Additionally, the percentage of patients with reduction in itch by ≥4 points was significantly higher for the dupilumab-treated patients compared to placebo (P<0.001).
Simpson et al.[40] (2017) SOLO 2	DB, MC, PC, RCT Patients ≥ 18 years of	N= 708 16 weeks	Primary: proportion of patients with IGA (0,1)	Primary: IGA (0,1) responses at week 16 were achieved by a significantly higher proportion of the dupilumab-treated patients.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dupilumab 300 mg SQ every week vs dupilumab 300 mg SQ every other week vs placebo	age with moderate-to-severe AD (IGA 3 or 4), inadequately controlled by topical treatment or medically inadvisable with AD ≥ three years		Secondary: EASI75 response, EASI50 response, reduction in itch by ≥4 points	The proportion of patients with IGA (0,1) response was 36% for the dupilumab 300 mg every two weeks and 36% for the dupilumab 300 mg every week compared to 8% for placebo (P<0.001). Secondary: There was a significantly greater improvement in secondary endpoints with dupilumab compared to placebo. A greater proportion of dupilumab-treated patients had EASI75 response compared to placebo at 48% and 44% to 12% (P<0.001). The percentage of patients with EASI50 was 61% and 65% for the dupilumab-treated patients compared to 22% for placebo (P<0.001). Additionally, the percentage of patients with reduction in itch by ≥4 points was significantly higher for the dupilumab-treated patients compared to placebo (P<0.001).
Blauvelt et al.[41] (2017) CHRONOS Dupilumab 300 mg SQ every week plus TCS vs dupilumab 300 mg SQ every other week plus TCS vs TCS	DB, MC, PC, RCT Patients ≥ 18 years of age with moderate-to-severe AD (IGA 3 or 4), inadequately controlled by topical treatment or medically inadvisable with AD ≥ three years	N= 740 52 weeks	Primary: proportion of patients with IGA (0,1) Secondary: EASI75 response, EASI50 response, reduction in itch by ≥4 points	Primary: IGA (0,1) responses at week 16 were achieved by a significantly higher proportion of the dupilumab with TCS-treated patients. The proportion of patients with IGA (0,1) response was 39% for the dupilumab 300 mg every week plus TCS group and 39% for the dupilumab 300 mg every other week plus TCS group compared to 12% for TCS group (P<0.001). Secondary: There was a significantly greater improvement in secondary endpoints with dupilumab plus TCS compared to TCS. A greater proportion of dupilumab plus TCS-treated patients had EASI75 response compared to TCS at 39% and 39% to 12% (P<0.0001). The percentage of patients with EASI50 was 64% and 69% for the dupilumab-treated patients compared to 23% for placebo (P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Additionally, the percentage of patients with reduction in itch by ≥4 points was significantly higher for the dupilumab-treated patients compared to placebo (P<0.0001).
Paller et al.[42] (2020) LIBERTY AD ADOL AD-1526 Dupilumab every 2 weeks: baseline weight of <60 kg, 400 mg at Week 0, followed by 200 mg every 2 weeks baseline weight of ≥60 kg, 600 mg at Week 0, followed by 300 mg every 2 weeks vs placebo Subjects were permitted to receive rescue treatment at the discretion of the investigator. Subjects who received rescue treatment were considered non-responders	DB, MC, PC, RCT Pediatric subjects 12 to 17 years of age with moderate-to-severe AD defined by an IGA score ≥3 (scale of 0 to 4), an EASI score ≥16 (scale of 0 to 72), and a minimum BSA involvement of ≥10%. Eligible subjects enrolled into this trial had previous inadequate response to topical medication.	N=251 16 weeks	Primary: Proportion of subjects with an IGA 0 (clear) or 1 (almost clear) and at least a 2-point improvement from baseline to Week 16. Secondary: The proportion of subjects with EASI-75 or EASI-90 (improvement of at least 75% or 90% in EASI from baseline, respectively), and reduction in itch as measured by the Peak Pruritus NRS (≥4-point improvement).	Primary: The proportion of subjects with an IGA 0 (clear) or 1 (almost clear) and at least a 2-point improvement from baseline to Week 16 in the dupilumab group was 24% compared to 2% for placebo group. Secondary: The proportion of subjects with EASI-75 was 42% in the dupilumab group compared to 8% for the placebo group. Regarding the proportion of subjects with EASI-90, 23% of the dupilumab group achieved this compared to 2% for the placebo group. Reduction in itch measured by the Peak Pruritus NRS (≥4-point improvement) was 37% for the dupilumab group compared to 5% for the placebo group.
Paller et al.[43] (2020) AD-1652	DB, MC, PC, RCT Subjects 6 to 11 years of age, with AD	N=367 16 weeks	Primary: Proportion of subjects with an IGA 0 (clear) or 1 (almost	Primary: The proportion of subjects with an IGA 0 (clear) or 1 (almost clear) from baseline to Week 16 in the dupilumab every 4-week group was 30% compared to 13% for placebo group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dupilumab every 4 weeks plus TCS: 600 mg day 1 followed by 300 mg every 4 weeks from week 4 to week 12, regardless of weight vs Dupilumab every 2 weeks + TCS (baseline weight < 30 kg: dupilumab 200 mg day 1 followed by 100 mg every 2 weeks week 2 to week 14; baseline weight ≥ 30 kg: dupilumab 400 mg day 1 followed by 200 mg every 2 weeks from week 2 to week 14. Subjects were permitted to receive rescue treatment at the discretion of the investigator. Subjects who received rescue treatment were considered non-responders	defined by an IGA score of 4 (scale of 0 to 4), an EASI score ≥21 (scale of 0 to 72), and a minimum BSA involvement of ≥15%. Eligible subjects enrolled into this trial had previous inadequate response to topical medication.		clear) at Week 16 Secondary: The proportion of subjects with EASI-75 or EASI-90 (improvement of at least 75% or 90% in EASI from baseline, respectively), and reduction in itch as measured by the Peak Pruritus NRS (≥4-point improvement).	The proportion of subjects with an IGA 0 (clear) or 1 (almost clear) from baseline to Week 16 in the dupilumab every 2-week group was 39% compared to 10% for placebo group. Secondary: The proportion of subjects with EASI-75 in the dupilumab every 4-week group was 75% compared to 28% for the placebo group. The proportion of subjects with EASI-75 in the dupilumab every 2-week group was 75% compared to 26% for the placebo group. Regarding the proportion of subjects with EASI-90, 46% of the dupilumab every 4-week group achieved this compared to 7% for the placebo group. In the dupilumab every 2-week group, 36% achieved an EASI-90 score compared to 8% in the placebo group. Reduction in itch measured by the Peak Pruritus NRS (≥4-point improvement) was 54% for the dupilumab every 4-week group compared to 12% for the placebo group. Comparatively, this was 61% for the dupilumab every 2-week group compared to 13% in the placebo group.
Paller et al.[44] (2022) Dupilumab every 4 weeks + TCS	DB, MC, PC, RCT Subjects 6 months to 5 years of age, with moderate-to-severe AD	N=162 16 weeks	Primary: Proportion of subjects with an IGA 0 (clear) or 1 (almost clear) at week 16	Primary: The proportion of subjects with an IGA 0 (clear) or 1 (almost clear) from baseline to Week 16 in the dupilumab every 4-week group was 28% compared to 4% for placebo group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(baseline weight ≥ 5 to < 15 kg: 200 mg day 1, followed by 200 mg every 4 weeks from week 4 to week 12; Baseline weight ≥ 15 to < 30 kg: 300 mg day 1, followed by 300 mg every 4 weeks from week 4 to week 12 vs placebo	defined by an IGA score ≥3 (scale of 0 to 4), an EASI score ≥16 (scale of 0 to 72), and a minimum BSA involvement of ≥10%. Eligible subjects enrolled into this trial had previous inadequate response to topical medication.		Secondary: Proportion of subjects with EASI-75 or EASI-90 and reduction in itch as measured by the Worst Scratch/Itch NRS (≥4-point improvement)	Secondary: The proportion of subjects with an EASI-75 score at week 16 was 53% for the dupilumab group compared to 11% for the placebo group. The proportion of subjects with an EASI-90 score at week 16 was 25% for the dupilumab group compared to 3% for the placebo group. Lastly, the proportion of subjects with a reduction in itch as measured by the Worst Scratch/Itch NRS (≥4-point improvement) was 48% for the dupilumab group compared to 9% for the placebo group.
Blauvelt et al.[45] (2021) Heads Up Upadacitinib 30 mg orally once daily vs dupilumab subcutaneous 300 mg every other week	DB, MC, RCT Adults 18 to 75 years of age with moderate-to-severe atopic dermatitis who were candidates for systemic therapy	N=692 24 weeks	Primary: EASI75 at week 16 Secondary: Efficacy endpoints at 16 and 24 weeks	Primary: At week 16, 247 patients receiving upadacitinib (71.0%) and 210 patients receiving dupilumab (61.1%) achieved EASI75 (P=0.006). Secondary: All ranked secondary end points also demonstrated the superiority of upadacitinib vs dupilumab, including improvement in Worst Pruritus NRS as early as week one (mean, 31.4% vs 8.8%; P<0.001), achievement of EASI75 as early as week two (152 vs 60; P<0.001), and achievement of EASI100 at week 16 (97 vs 26; P<0.001). A greater proportion of upadacitinib-treated than dupilumab-treated patients achieved EASI75 (223 of 348 [64.2%] vs 205 of 344 [59.2%]) at week 24. Upadacitinib-treated patients also had greater improvement from baseline in mean Worst Pruritus NRS than dupilumab-treated patients at week 24 (63.1% vs 54.7%).
Wollenberg et al.[46] (2021) ECZTRA 1 and ECZTRA 2 Tralokinumab 300 mg	DB, PC, RCT Adults with moderate-to-severe AD who had an inadequate response to topical treatments	N=802 (ECZTRA 1) N=792 (ECZTRA 2)	Primary: IGA score of 0 or 1 at week 16 and ≥ 75% improvement in EASI 75 at week 16	Primary: At week 16, more patients who received tralokinumab vs placebo achieved an IGA score of 0 or 1: 15.8% vs 7.1% in ECZTRA 1 [difference 8.6%; 95% CI, 4.1 to 13.1; P=0.002] and 22.2% vs 10.9% in ECZTRA 2 (11.1%; 95% CI, 5.8 to 16.4; P<0.001) and EASI 75: 25.0% vs 12.7% (12.1%; 95% CI, 6.5 to 17.7; P<0.001)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
subcutaneously every 2 weeks vs placebo	Patients achieving an IGA score of 0 or 1 and/or EASI 75 with tralokinumab at week 16 were rerandomized to tralokinumab every 2 weeks or every 4 weeks or placebo, for 36 weeks	52 weeks	Secondary: Maintenance outcomes at week 52	and 33.2% vs 11.4% (21.6%; 95% CI, 15.8 to 27.3; P<0.001). Secondary: In ECZTRA 1 and ECZTRA 2, 185 and 227 patients were rerandomized 2:2:1 to continue tralokinumab every two weeks, to reduce the dosing frequency of tralokinumab to every four weeks or to switch to placebo every two weeks. In patients who achieved IGA 0 or 1 with tralokinumab at week 16, IGA 0 or 1 was maintained at week 52 without rescue medication (including topical corticosteroids) in 51% with continued tralokinumab every two weeks vs 47% with tralokinumab every two weeks to placebo (difference 6.0%; 95% CI, −21.8 to 33.7; P=0.68) in ECZTRA 1 and in 59% with continued tralokinumab every two weeks vs 25% with tralokinumab every two weeks to placebo (difference 34.1%; 95% CI, 13.4 to 54.9; P=0.004) in ECZTRA 2. Early improvements in pruritus, sleep interference, Dermatology Life Quality Index, SCORing Atopic Dermatitis and Patient-Oriented Eczema Measure were observed from the first postbaseline measurements. The majority of week 16 tralokinumab responders maintained response at week 52 with continued tralokinumab treatment without any rescue medication (including topical corticosteroids). Adverse events were reported in 76.4% and 61.5% of patients receiving tralokinumab in ECZTRA 1 and ECZTRA 2, respectively, and in 77.0% and 66.0% of patients receiving placebo in ECZTRA 1 and ECZTRA 2, respectively, in the 16-week initial period.
Silverberg et al.[47] (2021) ECZTRA 3 Tralokinumab 300 mg subcutaneously every 2 weeks vs placebo	DB, MC, PC, RCT Adults with moderate-to-severe AD who were candidates for systemic therapy	N=380 32 weeks	Primary: IGA score of 0 (clear) or 1 (almost clear) and EASI 75 at week 16 Secondary: SCORing AD (SCORAD), weekly average of worst daily pruritus NRS ≥	Primary: An IGA score of 0/1 was achieved by 38.9% vs 26.2% (difference, 12.4%; 95% CI, 2.9 to 21.9; P=0.015) and EASI 75 by 56.0% vs 35.7% (difference, 20.2%; 95% CI, 9.8 to 30.6; P<0.001) for tralokinumab and placebo, respectively. Secondary: Tralokinumab improved all key secondary endpoints vs placebo. At week 16, a greater proportion of patients treated with tralokinumab vs those treated with placebo achieved a ≥ 4-point reduction in weekly average of worst daily pruritus NRS score:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
In combination with topical corticosteroids			4 and Dermatology Life Quality Index (DLQI) scores, all measuring change from baseline to week 16	45.4% vs 34.1% (11.3%; 95% CI, 0.9 to 21.6; P=0.037) and significant improvements in SCORAD score: –37.7 vs –26.8 (–10.9; 95% CI, –15.2 to –6.6; P<0.001) and total DLQI score: –11.7 vs –8.8 (–2.9; 95% CI, –4.3 to –1.6; P<0.001). Of the patients who were tralokinumab responders at week 16, 89.6% and 92.5% of those treated with tralokinumab every two weeks and 77.6% and 90.8% treated with tralokinumab every four weeks maintained an IGA 0/1 and EASI 75 response at week 32, respectively. Among patients who did not achieve IGA 0/1 and EASI 75 with tralokinumab every two weeks at 16 weeks, 30.5% and 55.8% achieved these endpoints, respectively, at week 32.
Paller et al.[48] (2023) ECZTRA 6 Tralokinumab (150 or 300 mg) every 2 weeks for 16 weeks vs placebo for 16 weeks Patients with an IGA score of 0 (clear) or 1 (almost clear) and/or 75% or higher improvement in EASI (EASI 75) at week 16 without rescue medication received maintenance treatment; other patients switched to open-label tralokinumab, 300 mg, every two weeks	DB, MC, PC, RCT Patients were 12 to 17 years old with moderate to severe AD (IGA score ≥3; Eczema Area and Severity Index [EASI] ≥16)	N=301 52 weeks	Primary: IGA score of 0 or 1 and/or achieving EASI 75 at week 16 Secondary: reduction of Adolescent Worst Pruritus Numeric Rating Scale of 4 or more, change in SCORing AD, and change in Children's Dermatology Life Quality Index from baseline to week 16	Primary: More patients receiving tralokinumab 150 mg and tralokinumab 300 mg achieved an IGA score of 0 or 1 without rescue medication at week 16 (21.4% and 17.5%, respectively) vs placebo (4.3%) (adjusted difference, 17.5%; 95% CI, 8.4% to 26.6%; P<0.001 and 13.8%; 95% CI, 5.3% to 22.3%; P=0.002, respectively). More patients receiving tralokinumab, 150 mg (28.6%), and tralokinumab, 300 mg, (27.8%) vs placebo (6.4%) achieved EASI 75 without rescue at week 16 (adjusted difference, 22.5%; 95% CI, 12.4% to 32.6%; P<0.001 and 22.0%; 95% CI, 12.0% to 32.0%; P<0.001, respectively). Secondary: Proportions of patients with Adolescent Worst Pruritus Numeric Rating Scale reduction of 4 or more from baseline were greater with tralokinumab, 150 mg (23.2%), and tralokinumab, 300 (25.0%), vs placebo (3.3%), and adjusted mean changes were greater in SCORing AD with tralokinumab, 150 mg (-27.5), and tralokinumab, 300 mg (-29.1), vs placebo (-9.5) and in Children's Dermatology Life Quality Index with tralokinumab, 150 mg (-6.1), and tralokinumab, 300 mg (-6.7), vs placebo (-4.1) at week 16. At week 52, tralokinumab efficacy was maintained without rescue in more than 50% of patients meeting primary end point(s) at week 16. In the open-label phase, IGA score of 0 or 1 and EASI 75 were achieved in 33.3% and 57.8%, respectively, at

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				week 52.
Axial Spondyloarthritis (Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis)				
Dougados et al.[49] (2020) COAST-V and COAST-W Ixekizumab 80 mg every 2 (IXE Q2W) or 4 weeks (IXE Q4W), placebo (PBO) vs adalimumab 40 mg Q2W (ADA) in COAST-V Ixekizumab Q2W, Ixekizumab Q4W or PBO in COAST-W At week 16, patients receiving ixekizumab continued their assigned treatment; patients receiving PBO or ADA were re-randomized 1:1 to IXE Q2W or IXE Q4W (PBO/IXE, ADA/IXE) through week 52	DB, MC, RCT Adults with active radiographic axial spondyloarthritis (r-axSpA) who were biological disease-modifying antirheumatic drug (bDMARD)-naive (COAST-V) or tumour necrosis factor inhibitor (TNFi)-experienced (COAST-W)	N=341 in COAST-V N=316 in COAST-W 52 weeks	Primary: ASAS, ASDAS, and additional scores Secondary: Safety	Primary: Week 52 ASAS40 response rates were 53.1% (IXE Q4W) and 50.6% (IXE Q2W) in COAST-V and 34.2% (IXE Q4W) and 30.6% (IXE Q2W) in COAST-W. Patients randomized to PBO and re-randomized to ixekizumab at week 16 (PBO/IXE) showed rapid improvement in ASAS40 response rates after switching to ixekizumab; week 52 response rates (46.5% in COAST-V, 38.7% in COAST-W) were numerically similar to those in patients initially randomized to ixekizumab. In COAST-V, patients randomized to ADA showed further numerical improvements in ASAS40 response rates (36.0% at week 16, 51.2% at week 52) after switching to ixekizumab; week 52 response rates were numerically similar to those in patients initially randomized to ixekizumab. Among ADA/IXE patients who were ASAS40 non-responders at week 16, but ASAS40 responders at week 52, 47.4% were ASAS20 non-responders and 52.6% were ASAS20 responders at week 16. Secondary: In the extended treatment population (weeks 16 to 52), 201 (61.1%) patients in COAST-V and 179 (63.7%) patients in COAST-W reported treatment-emergent adverse events (TEAEs). Most TEAEs were of mild or moderate severity. Eight (2.4%) patients in COAST-V and 10 (3.6%) patients in COAST-W discontinued treatment because of an adverse event. The most common TEAEs were nasopharyngitis, injection site reactions and upper respiratory tract infection.
Deodhar et al.[50] (2020) COAST-X Ixekizumab 80 mg	DB, MC, PC, RCT Adults with active axial spondyloarthritis without definite	N=303 52 weeks	Primary: ASAS40 response at week 16 and 52 Secondary:	Primary: Thirty-five percent of patients in the ixekizumab Q4W group (P=0.0094 vs placebo), 40% of patients in the ixekizumab Q2W group (P=0.0016 vs placebo), and 19% of patients in the placebo group achieved ASAS40 at week 16. Thirty percent of patients in

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subcutaneous every 4 weeks (Q4W) or every 2 weeks (Q2W) vs placebo	radiographic sacroiliitis (non-radiographic axial spondyloarthritis), objective signs of inflammation (via MRI or C-reactive protein), and an inadequate response or intolerance to non-steroidal anti-inflammatory drugs (NSAIDs)		ASDAS-CRP, BASDAI, Spondyloarthritis Research Consortium of Canada (SPARCC) MRI of the sacroiliac joints; safety	the ixekizumab Q4W group (P=0.0045 vs placebo), 31% of patients in the ixekizumab Q2W group (P=0.0037 vs placebo), and 13% of patients in the placebo group achieved ASAS40 at week 52. Secondary: All the major secondary endpoints included in the multiple testing scheme showed greater improvements in each ixekizumab treatment group than in the placebo group at weeks 16 and 52. Patients in each ixekizumab treatment group had greater reductions in disease activity, shown by the change from baseline in ASDAS and BASDAI, and had greater improvements in SF-36 PCS scores than did patients in the placebo group. More patients in the ixekizumab groups achieved ASDAS low disease activity and showed greater reductions in sacroiliac joints SPARCC scores than did those on placebo. Decreases in CRP (a non-multiplicity-adjusted endpoint) were larger in both ixekizumab groups than in the placebo group at weeks 16 and 52, although differences did not reach statistical significance. In the safety population (n=302), 60 (57%) of 104 patients in the placebo group, 63 (66%) of 96 in the ixekizumab Q4W group, and 79 (77%) of 102 in the ixekizumab Q2W group had at least one treatment-emergent adverse event. Four (1%) of 302 patients had at least one serious adverse event. The frequencies of serious adverse events and discontinuations due to adverse events were similar across the three groups. The most common treatment-emergent adverse events in the ixekizumab groups were nasopharyngitis and injection site reaction.
Chronic rhinosinusitis with nasal polyps				
Bachert et al.[51] (2019) LIBERTY NP SINUS-24 & LIBERTY NP SINUS-52 SINUS-24:	DB, MC, PC, PG, RCT Patients were 18 years or older with bilateral CRSwNP and symptoms despite intranasal corticosteroid	SINUS-24 N=276 24 weeks SINUS-52 N=448	Primary: Changes from baseline to week 24 in NPS, nasal congestion or obstruction, and sinus Lund-Mackay	Primary: At 24 weeks, least squares mean difference in NPS of dupilumab treatment versus placebo was -2.06 (95% CI, -2.43 to -1.69; P<0.0001) in SINUS-24 and -1.80 (-2.10 to -1.51; P<0.0001) in SINUS-52; difference in nasal congestion or obstruction score was -0.89 (-1.07 to -0.71; P<0.0001) in SINUS-24 and -0.87 (-1.03 to -0.71; P<0.0001) in SINUS-52; and difference in Lund-

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dupilumab 300 mg SC every 2 weeks vs placebo every 2 weeks SINUS-52 dupilumab 300 mg every 2 weeks for 52 weeks vs dupilumab every 2 weeks for 24 weeks and then every 4 weeks for the remaining 28 weeks vs placebo every 2 weeks for 52 weeks.	use, receiving systemic corticosteroids in the preceding 2 years, or having had sinonasal surgery.	52 weeks	CT scores, done in an intention-to-treat population. Secondary: Change from baseline at week 24 in sinus opacification, assessed by Lund-Mackay CT score; patient-reported total symptom score (a composite severity score consisting of the sum of daily symptoms of nasal congestion, loss of smell, and anterior or posterior rhinorrhea); daily loss of smell or smell impairment; SNOT-22 score; and UPSIT smell test. Multiplicity-tested key secondary endpoints for SINUS-52 were change from baseline at week 52 in NPS, nasal congestion, and SNOT-22 score (group A alone). NPS and Lund-Mackay CT scan scoring was done centrally by masked	Mackay CT scores was -7.44 (-8.35 to -6.53; P<0.0001) in SINUS-24 and -5.13 (-5.80 to -4.46; P<0.0001) in SINUS-52. Secondary: All multiplicity-adjusted key secondary endpoints showed significant and clinically relevant improvements with dupilumab treatment (P<0.0001 in both studies), with all effects having an early onset (in the first 2 to 4 weeks of treatment). Patients treated with dupilumab in SINUS-52 had progressive improvement up to week 52, whereas symptoms worsened after discontinuation of dupilumab at week 24 in patients in SINUS-24. Lund-Mackay CT scores improved significantly in dupilumab groups at week 24 compared with those of placebo groups, with improvements seen in all sinuses. Improvements in SNOT-22 scores with dupilumab treatment exceeded the minimal clinically important difference of an 8.9-point improvement or higher and were significant compared with those with placebo. Results of the UPSIT smell test showed that the proportion of patients with anosmia (UPSIT score of ≤18) in the dupilumab groups decreased in SINUS-24 from 104 (74%) of 140 patients at baseline to 33 (24%) of 138 at week 24 and in SINUS-52 from 228 (79%) of 287 patients to 84 (30%) of 280 at week 24, with almost no change observed in the placebo group

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			review of the video recordings of standardized endoscopies (for NPS) and sinus images (for Lund-Mackay CT).	
Crohn's Disease/ Ulcerative Colitis				
D'Haens et al.[52] (2022) ADVANCE and MOTIVATE Risankizumab 600 mg vs risankizumab 1200 mg vs placebo	DB, PC, RCT Eligible patients aged 16 to 80 years with moderately to severely active Crohn's disease, previously showing intolerance or inadequate response to one or more approved biologics or conventional therapy (ADVANCE) or to biologics (MOTIVATE), were randomly assigned to receive a single dose of intravenous risankizumab (600 mg or 1200 mg) or placebo (2:2:1 in ADVANCE, 1:1:1 in MOTIVATE) at weeks 0, 4, and 8.	N=1,549 12 weeks	Primary: clinical remission and endoscopic response at week 12 Secondary: Safety and adverse effects	Primary: Participants were enrolled between May 10, 2017, and Aug 24, 2020 (ADVANCE trial), and Dec 18, 2017 and Sept 9, 2020 (MOTIVATE trial). In ADVANCE, 931 patients were assigned to either risankizumab 600 mg (n=373), risankizumab 1200 mg (n=372), or placebo (n=186). In MOTIVATE, 618 patients were assigned to risankizumab 600 mg (n=206), risankizumab 1200 mg (n=205), or placebo (n=207). The primary analysis population comprised 850 participants in ADVANCE and 569 participants in MOTIVATE. All coprimary endpoints at week 12 were met in both trials with both doses of risankizumab (p values ≤0.0001). In ADVANCE, CDAI clinical remission rate was 45% (adjusted difference 21%, 95% CI 12-29; 152/336) with risankizumab 600 mg and 42% (17%, 8-25; 141/339) with risankizumab 1200 mg versus 25% (43/175) with placebo; stool frequency and abdominal pain score clinical remission rate was 43% (22%, 14-30; 146/336) with risankizumab 600 mg and 41% (19%, 11-27; 139/339) with risankizumab 1200 mg versus 22% (38/175) with placebo; and endoscopic response rate was 40% (28%, 21-35; 135/336) with risankizumab 600 mg and 32% (20%, 14-27; 109/339) with risankizumab 1200 mg versus 12% (21/175) with placebo. In MOTIVATE, CDAI clinical remission rate was 42% (22%, 13-31; 80/191) with risankizumab 600 mg and 40% (21%, 12-29; 77/191) with risankizumab 1200 mg versus 20% (37/187) with placebo; stool frequency and abdominal pain score clinical remission rate was 35% (15%, 6-24; 66/191) with risankizumab 600 mg and 40% (20%, 12-29; 76/191) with risankizumab 1200 mg versus 19% (36/187) with placebo; and endoscopic response rate was 29% (18%, 10-25; 55/191) with risankizumab 600 mg

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				and 34% (23%, 15-31; 65/191) with risankizumab 1200 mg versus 11% (21/187) with placebo. Secondary: The overall incidence of treatment-emergent adverse events was similar among the treatment groups in both trials. Three deaths occurred during induction (two in the placebo group [ADVANCE] and one in the risankizumab 1200 mg group [MOTIVATE]). The death in the risankizumab-treated patient was deemed unrelated to the study drug.
Ferrante et al.[53] (2022) FORTIFY Risankizumab 180 mg subcutaneous every 8 weeks vs risankizumab 360 mg subcutaneous every 8 weeks vs placebo	DB, MC, PC, RCT Participants with clinical response to risankizumab in the ADVANCE or MOTIVATE induction studies	N=542 52 weeks	Primary: Clinical remission and endoscopic response at week 52 Secondary: Stool frequency remission, abdominal pain remission, CDAI clinical response, enhanced stool frequency and abdominal pain score clinical response, ulcer-free endoscopy (i.e., absence of ulceration), endoscopic remission, composite endpoint of clinical remission and endoscopic response, CDAI deep remission (i.e., composite of clinical remission and endoscopic	Primary: Greater clinical remission and endoscopic response rates were reached with 360 mg risankizumab versus placebo (CDAI clinical remission was reached in 74 (52%) of 141 patients vs 67 (41%) of 164 patients, adjusted difference 15% (95% CI, 5 to 24); stool frequency and abdominal pain score clinical remission was reached in 73 (52%) of 141 vs 65 (40%) of 164, adjusted difference 15% (95% CI, 5 to 25); endoscopic response 66 (47%) of 141 patients vs 36 (22%) of 164 patients, adjusted difference 28% (95% CI, 19 to 37). Secondary: Higher rates of CDAI clinical remission and endoscopic response (but not stool frequency and abdominal pain score clinical remission [p=0.124]) were also reached with risankizumab 180 mg versus withdrawal (subcutaneous placebo; CDAI clinical remission reached in 87 [55%] of 157 patients, adjusted difference 15% [95% CI, 5 to 24]; endoscopic response 74 [47%] of 157, adjusted difference 26% [95% CI, 17 to 35]).

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			remission), stool frequency and abdominal pain score clinical response at week 52	
Sands et al.[54] (2022) SEAVUE Ustekinumab (approximately 6 mg/kg intravenously on day 0, then 90 mg subcutaneously once every 8 weeks) vs adalimumab (160 mg on day 0, 80 mg at 2 weeks, then 40 mg once every 2 weeks, subcutaneously)	AC, DB, RCT Biologic-naïve patients aged 18 years or older with moderately to severely active Crohn's disease and a Crohn's Disease Activity Index (CDAI) score of 220-450, who had not responded to or were intolerant to conventional therapy (or were corticosteroid dependent) and had at least one ulcer of any size at baseline endoscopic evaluation	N=386 52 weeks	Primary: Proportion of patients who were in clinical remission (CDAI score <150) at week 52 Secondary: Safety	Primary: There was no significant difference between the ustekinumab and adalimumab groups in the occurrence of the primary endpoint; at week 52, 124 (65%) of 191 patients in the ustekinumab group versus 119 (61%) of 195 in the adalimumab group were in clinical remission (between-group difference, 4%; 95% CI, -6 to 14; P=0.42). Secondary: Safety for both groups was consistent with previous reports. Serious infections were reported in four (2%) of 191 patients in the ustekinumab group and five (3%) of 195 in the adalimumab group. No deaths occurred through week 52 of the study.
Sands et al.[55] (2019) UNIFI Ustekinumab subcutaneous maintenance injections of 90 mg (either every 12 weeks [172 patients] or every 8 weeks [176]) vs	DB, PC, RCT Patients with moderate-to-severe ulcerative colitis who had a response to induction therapy 8 weeks after administration of intravenous ustekinumab were randomly assigned to treatment or placebo	N=961 52 weeks (8-week randomized induction and 44-week randomized-withdrawal maintenance)	Primary: Clinical remission Secondary: Endoscopic improvement, clinical response	Primary: Of 961 patients who underwent randomization, 912 (94.9%) completed the induction trial: 783 (81.5%) who entered the maintenance trial and 129 (13.4%) who did not enter the maintenance trial completed the final safety visit. Induction therapy: At week 8, the percentages of patients in clinical remission were higher in the groups that received ustekinumab at a dose of either 130 mg (15.6% [50 of 320 patients]) or 6 mg per kilogram (15.5% [50 of 322]) than in the placebo group (5.3% [17 of 319]) (P<0.001 for both comparisons with placebo).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				Maintenance therapy: Among patients who had a clinical response to induction treatment with ustekinumab, the percentages of patients who had clinical remission at week 44 (52 weeks after intravenous induction) were significantly higher in the groups that received 90 mg of ustekinumab every 12 weeks (38.4% [66 of 172 patients]) or every 8 weeks (43.8% [77 of 176]) than in the placebo group (24.0% [42 of 175]) (P=0.002 and P<0.001, respectively, for the comparison with placebo). Secondary: The percentages of patients with maintenance of clinical response through week 44, endoscopic improvement at week 44, or corticosteroid-free clinical remission (with either definition of clinical remission) at week 44 were significantly higher in both ustekinumab groups than in the placebo group (Figure 3).
Eosinophilic esophagitis				
Dellon at al.[56] (2022) Part A: Dupilumab 300 mg SC weekly vs placebo Part B: Dupilumab 300 mg SC weekly vs dupilumab 300 mg SC every 2 weeks	DB, PC, PG, MC, RCT Adults and pediatric patients 12 to 17 years of age, weighing at least 40 kg, with EoE. Eligible patients had ≥ 15 intraepithelial eosinophils per high-power field (eos/hpf) following a treatment course of a proton pump inhibitor either prior to or during the screening period and symptoms of dysphagia as measured by the DSQ	24 weeks	Primary: Proportion of patients achieving histological remission defined as peak esophageal intraepithelial eosinophil count of ≤ 6 eos/hpf at week 24; and the absolute change in the subject-reported DSQ score from baseline to week 24 Key secondary: The percentage change from baseline in the peak esophageal	Primary: In Part A, histologic remission occurred in 25 of 42 patients (60%) who received weekly dupilumab and in 2 of 39 patients (5%) who received placebo (difference, 55 percentage points; 95% confidence interval [CI], 40 to 71; P<0.001). In Part B, histologic remission occurred in 47 of 80 patients (59%) with weekly dupilumab, in 49 of 81 patients (60%) with dupilumab every 2 weeks, and in 5 of 79 patients (6%) with placebo (difference between weekly dupilumab and placebo, 54 percentage points; 95% CI, 41 to 66 [P<0.001]; difference between dupilumab every 2 weeks and placebo, 56 percentage points; 95% CI, 43 to 69 [not significant per hierarchical testing]) Secondary: Part A: The percentage of patients who had < 15 eos/hpf was greater among those who received weekly dupilumab than among those who received placebo, with an adjusted between-group difference of 58 percentage points (95% CI, 42 to 73; P<0.001). The reduction from baseline in peak eosinophil count at week 24 was greater among those who received weekly dupilumab than

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vs placebo			intraepithelial eosinophil count; the absolute change from baseline in the grade and stage scores on the Eosinophilic Esophagitis Histology Scoring System (EoE-HSS	among those who received placebo, with a least-squares (LS) mean between-group difference of –68.3 percentage points (95% CI, –86.9 to –49.6; P<0.001). Part B: The adjusted difference among patients with < 15 eos/hpf at week 24 between those who received weekly dupilumab and those who received placebo was 75 percentage points (95% CI, 64 to 86), and the corresponding value between those who received dupilumab every 2 weeks and those who received placebo was 72 percentage points (95% CI, 61 to 84). The LS mean difference in the change from baseline in peak eosinophil count at week 24 between the patients who received weekly dupilumab and those who received placebo was –88.6 percentage points (95% CI, –112.2 to –65.0), and the corresponding value between the patients who received dupilumab every 2 weeks and those who received placebo was –79.2 percentage points (95% CI, –103.1 to –55.3). Part A: A reduction from baseline in the EoE-HSS grade score at week 24 was observed among the patients who received weekly dupilumab as compared with those who received placebo (least-squares mean between-group difference, –0.76 points [95% CI, –0.91 to –0.61, P<0.001]), as was a reduction from baseline in the EoE-HSS stage score (LS mean between-group difference, –0.74 points [95% CI, –0.88 to –0.60, P<0.001]). Part B: the least-squares mean difference in the EoE-HSS grade score between the patients who received weekly dupilumab and those who received placebo was –0.68 points (95% CI, –0.79 to –0.57), and the corresponding value between the patients who received dupilumab every 2 weeks and those who received

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				placebo was –0.67 points (95% CI, –0.78 to –0.55). The LS mean difference in the EoE-HSS stage score between the patients who received weekly dupilumab and those who received placebo was –0.67 points (95% CI, –0.78 to –0.57), and the corresponding value between the patients who received dupilumab every 2 weeks and those who received placebo was –0.66 points (95% CI, –0.77 to –0.55).
Prurigo Nodularis				
Yosipovitch et al.[57] (2023) LINERTY-PN PRIME and PRIME2 Dupilumab 600 mg on day 1 followed by 300 mg every other week Vs Placebo Patients on a stable regimen of low-to-moderate potency TCSs and TCIs before screening were allowed to continue their use throughout the trial.	DB, PC, PG, MC, RCT Adults 18 years of age and older with pruritus (WI-NRS ≥ 7 on a scale of 0 to 10) and greater than or equal to 20 nodular lesions.	N=311 (PRIME:151, PRIME2:160) 24 weeks	Primary: Pruritus improvement, measured by proportion of patients with a ≥4-point reduction in Worst Itch Numeric Rating Scale (WI-NRS) from baseline at week 24 (PRIME) or week 12 (PRIME2). Key secondary: Nodule number reduction to ≤5 at week 24	Primary: A ≥4-point WI-NRS reduction at week 24 in the dupilumab and placebo arms was achieved by 60.0% and 18.4% of patients, respectively, in PRIME (95% confidence interval (CI), 27.8–57.7 for the difference, *P*< 0.001) and at week 12 by 37.2% and 22.0% of patients, respectively, in PRIME2 (95% CI, 2.3–31.2; *P*=0.022). Secondary: Significantly more dupilumab-treated patients achieved an IGA PN-S score of 0 or 1 (‘clear’ or ‘almost clear’, ≤5 nodules) in each trial at week 24: PRIME, 48.0% versus 18.4% (95% CI for the difference, 13.4 to 43.2; *P*<0.001); PRIME2, 44.9% versus 15.9% (95% CI for the difference, 16.4 to 45.2; *P*<0.001). At week 12, this endpoint was achieved by 32.0% versus 11.8% of patients in PRIME (95% CI for the difference, 7.8 to 34.0; non-multiplicity-controlled *P*=0.003) and 25.6% versus 12.2% in PRIME2 (95% CI for the difference, 2.6 to 27.0; *P*=0.01
Psoriasis				
Gordon et al.[58] (2021) BE READY Bimekizumab 320 mg every 4 weeks vs	DB, MC, PC, RCT Adults with moderate to severe plaque psoriasis	N=435 56 weeks	Primary: PASI90 and IGA of 0/1 at week 16 Secondary: Other levels of improved PASI and IGA at different time	Primary: Coprimary endpoints were met: at week 16, 317 (91%) of 349 patients receiving bimekizumab 320 mg every 4 weeks achieved PASI90, compared with one (1%) of 86 patients receiving placebo (risk difference, 89.8; 95% CI, 86.1 to 93.4; P<0.0001); and 323 (93%) of 349 patients receiving bimekizumab 320 mg every 4 weeks achieved an IGA score of 0 or 1 versus one (1%) of 86 patients receiving placebo (risk difference. 91.5; 95% CI,

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placebo Bimekizumab-treated patients achieving PASI90 at week 16 were re-allocated (1:1:1) to receive bimekizumab 320 mg every 4 weeks, every 8 weeks, or placebo for weeks 16 to 56			points; safety	88.0 to 94.9; P<0.0001). Secondary: Completely clear skin at week 16, as measured by PASI100, was achieved by 238 (68%) of 349 patients in the bimekizumab 320 mg every 4 weeks group; in the placebo group, one (1%) of 86 patients achieved PASI100 (P<0.0001). In the group receiving bimekizumab 320 mg every 4 weeks, 243 (70%) of 349 patients achieved an IGA score of 0, compared with one (1%) of 86 patients in the placebo group (P<0.0001). At week 16, improvements in scalp IGA (score 0 or 1) were also seen in patients with scalp psoriasis treated with bimekizumab 320 mg every 4 weeks compared with those treated with placebo (P<00001). Responses were maintained through to week 56 with bimekizumab 320 mg every 8 weeks and every 4 weeks. Treatment-emergent adverse events in the initial treatment period (up to week 16) were reported in 213 (61%) of 349 patients receiving bimekizumab 320 mg every 4 weeks and 35 (41%) of 86 patients receiving placebo every 4 weeks. From week 16 to week 56, treatment-emergent adverse events were reported in 78 (74%) of 106 patients receiving bimekizumab 320 mg every 4 weeks, 77 (77%) of 100 patients receiving bimekizumab 320 mg every 8 weeks, and 72 (69%) of 105 patients receiving placebo.
Reich et al.[59] (2021) BE VIVID Bimekizumab 320 mg every 4 weeks vs ustekinumab 45 mg or 90 mg (baseline weight-dependent dosing) at	DB, MC, RCT Adults with moderate to severe plaque psoriasis (PASI score ≥12, ≥10% BSA affected by psoriasis, and IGA score ≥3 on a five point scale)	N=567 52 weeks	Primary: PASI90 and IGA of 0/1 at week 16 Secondary: Other levels of improved PASI and IGA at different time points; safety	Primary: At week 16, 273 (85%) of 321 patients in the bimekizumab group had PASI90 versus 81 (50%) of 163 in the ustekinumab group (risk difference, 35; 95% CI, 27 to 43; P<0.0001) and four (5%) of 83 in the placebo group (risk difference, 80; 95% CI, 74 to 86; P<0.0001). At week 16, 270 (84%) patients in the bimekizumab group had an IGA response versus 87 (53%) in the ustekinumab group (risk difference, 30; 95% CI, 22 to 39; P<0.0001) and four (5%) in the placebo group (risk difference, 79; 95% CI, 73 to 85; P<0.0001). Secondary:

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weeks 0 and 4, then every 12 weeks vs placebo every 4 weeks At week 16, patients receiving placebo switched to bimekizumab 320 mg every 4 weeks				More patients receiving bimekizumab had complete skin clearance (PASI100) at week 16 than patients receiving ustekinumab (nominal P<0.0001) or placebo (P<0.0001). Likewise, more patients receiving bimekizumab had an IGA score of 0 at week 16 than patients in the ustekinumab group (nominal P<0.0001) or the placebo group (P<0.0001). At week 16, more patients in the bimekizumab group with a scalp IGA score at baseline of 2 or more had a scalp IGA response than patients in the ustekinumab group (nominal P=0.0004) or the placebo group (P<0.0001). Responses were maintained up to and including week 52 with bimekizumab treatment. At week 52, a higher proportion of patients receiving bimekizumab had PASI90 than patients receiving ustekinumab (P<0.0001), and more patients had an IGA response in the bimekizumab group than in the ustekinumab group (P<0.0001). At week 52, 207 (65%) of 321 patients in the bimekizumab group had PASI100 compared with 62 (38%) of 163 in the ustekinumab group (nominal P<0.0001). Over 52 weeks, serious treatment-emergent adverse events were reported in 24 (6%) of 395 patients in the bimekizumab group (including those who switched from placebo at week 16) and 13 (8%) of 163 in the ustekinumab group.
Warren et al.[60] (2021) BE SURE Bimekizumab 320 mg every 4 weeks for 56 weeks vs bimekizumab 320 mg every 4 weeks for 16 weeks, then every 8 weeks for weeks 16 to 56	DB, MC, RCT Adults with plaque psoriasis for at least 6 months before screening, and had moderate-to-severe plaque psoriasis at screening and baseline	N=478 56 weeks (16-week initial treatment period, and a 40-week maintenance treatment period)	Primary: PASI90 and IGA of 0/1 at week 16 Secondary: Five ranked secondary efficacy end points were a PASI 100 response (complete skin clearance) at week 16, a PASI 75 response (≥75% reduction from baseline in the PASI score) at week 4, a	Primary: At week 16, a total of 275 of 319 patients (86.2%) who received bimekizumab (both dose groups combined) and 75 of 159 (47.2%) who received adalimumab had a PASI 90 response (adjusted risk difference, 39.3 percentage points; 95% CI, 30.9 to 47.7; P<0.001 for noninferiority and superiority). A total of 272 of 319 patients (85.3%) who received bimekizumab and 91 of 159 (57.2%) who received adalimumab had an IGA score of 0 or 1 (adjusted risk difference, 28.2 percentage points; 95% CI, 19.7 to 36.7; P<0.001 for noninferiority and superiority). Secondary: With respect to secondary end points, 194 of 319 patients (60.8%) receiving bimekizumab had a PASI 100 response (complete skin clearance) at week 16, as compared with 38 of 159 (23.9%) receiving adalimumab (adjusted risk difference, 37.0 percentage

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs adalimumab subcutaneous at a dose of 40 mg every 2 weeks for 24 weeks, followed by bimekizumab at a dose of 320 mg every 4 weeks to week 56			PASI 100 response at week 24, a PASI 90 response at week 24, and an IGA score of 0 or 1 at week 24; safety	points; 95% CI, 28.6 to 45.3; P<0.001). At week 4, after one dose of treatment, 244 of 319 patients (76.5%) receiving bimekizumab had a PASI 75 response, as compared with 50 of 159 (31.4%) receiving adalimumab (adjusted risk difference, 44.8 percentage points; 95% CI, 36.3 to 53.4; P<0.001). The percentages of patients with a PASI 100 response, a PASI 90 response, and an IGA score of 0 or 1 at week 24 were significantly higher with bimekizumab than with adalimumab. The most common adverse events with bimekizumab were upper respiratory tract infections, oral candidiasis (predominantly mild or moderate as recorded by the investigator), hypertension, and diarrhea.
Reich et al.[61] (2021) BE RADIANT Bimekizumab subcutaneously at a dose of 320 mg every 4 weeks vs secukinumab subcutaneously at a dose of 300 mg weekly to week 4, followed by every 4 weeks to week 48 At week 16, patients receiving bimekizumab underwent re-randomization, in a 1:2 ratio, to receive maintenance dosing every 4 weeks or every 8 weeks to week 48.	AC, DB, MC, RCT Adults with plaque psoriasis for at least 6 months before screening and had moderate-to-severe plaque psoriasis at screening and baseline	N=743 48 weeks	Primary: PASI100 at week 16 Secondary: The ranked secondary efficacy end points were PASI 75 (≥75% reduction from baseline score) at week 4 and PASI 100 at week 48, which was evaluated on the basis of all patients assigned to bimekizumab, followed by separate tests for the bimekizumab every-4-week and every-8-week maintenance treatment regimens	Primary: At week 16, a total of 230 patients (61.7%) in the bimekizumab group and 181 (48.9%) in the secukinumab group had a 100% reduction from baseline in the PASI score (PASI 100) (adjusted risk difference, 12.7 percentage points; 95% CI, 5.8 to 19.6); bimekizumab was shown to be noninferior and superior to secukinumab (P<0.001 for noninferiority and superiority). Secondary: At week 48, a total of 250 patients (67.0%) treated with bimekizumab had a PASI 100 response, as compared with 171 patients (46.2%) treated with secukinumab (adjusted risk difference, 20.9 percentage points; 95% CI, 14.1 to 27.7; P<0.001). At the week 4 time point, 265 patients (71.0%) in the bimekizumab group had 75% or greater reduction from baseline in the PASI score, as compared with 175 patients (47.3%) in the secukinumab group (adjusted risk difference, 23.7; 95% CI, 17.0 to 30.4; P<0.001). Oral candidiasis occurred more often with bimekizumab (72 patients, 19.3%) than with secukinumab (11 patients, 3.0%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Gordon et al.[62,63] (2015) UNCOVER-1 Induction phase ixekizumab 80 mg SQ every two weeks vs ixekizumab 80 mg SQ every four weeks vs placebo SQ every two weeks Maintenance phase ixekizumab 80 mg SQ every four weeks vs ixekizumab 80 mg SQ every 12 weeks vs placebo SQ every four weeks	DB, MC, PC, RCT Patients ≥ 18 years of age with a minimum BSA involvement of 10%, PASI score of ≥12, sPGA ≥3 and candidates for phototherapy or systemic therapy	N= 1,296 60 weeks	Primary: PASI75 response, sPGA (0,1) with ≥2-point improvement from baseline Secondary: sPGA (0), PASI90, PASI100, change in DLQI, change in NAPSI, improvement in itching based on NRS	Primary: PASI75 and sPGA (0,1) responses at week 12 were achieved by a significantly higher proportion of the ixekizumab-treated patients. Response rates associated with 80 mg every two weeks were numerically superior to those associated with 80 mg every four weeks. The proportion of patients with PASI75 response was 89.1% for the 80 mg every two weeks and 82.6% for the 80 mg every four weeks compared to 3.9% for placebo (P<0.001). The proportion of patients with sPGA (0,1) was 81.8% for the 80 mg every two weeks and 76.4% for the 80 mg every four weeks compared to 3.2% for placebo (P<0.001). For week 12 responders to ixekizumab, efficacy in terms of PASI 75 and sPGA (0,1) was maintained through the 60-week maintenance period compared to placebo (P values not reported). Secondary: There was a significantly greater improvement in secondary endpoints with ixekizumab compared to placebo. Response rates associated with 80 mg every two weeks were numerically superior to those associated with 80 mg every four weeks. A greater proportion of ixekizumab-treated patients had sPGA (0) response compared to placebo at 37.0% and 34.5% to 0% (P<0.001). The percentage of patients with PASI90 was 70.9% and 64.6% for the ixekizumab-treated patients compared to 0.5% for placebo (P<0.001). Additionally, the percentage of patients with PASI100 was 35.5% and 33.6% for the ixekizumab-treated patients compared to 0% for placebo (P<0.001). Patients in both ixekizumab groups reported significant improvements in DLQI, NAPSI and itching by week 12 compared to placebo groups (P<0.001 for all endpoints).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Griffiths et al.[62,63] (2015) UNCOVER-2 Induction phase ixekizumab 80 mg SQ every two weeks vs ixekizumab 80 mg SQ every four weeks vs etanercept 50 mg SQ twice weekly vs placebo SQ every two weeks Maintenance phase ixekizumab 80 mg SQ every four weeks vs ixekizumab 80 mg SQ every 12 weeks vs	DB, MC, PC, RCT Patients ≥ 18 years of age with a minimum BSA involvement of 10%, PASI score of ≥12, sPGA ≥3 and candidates for phototherapy or systemic therapy	N= 1,224 60 weeks	Primary: PASI75 response, sPGA (0,1) with ≥2-point improvement from baseline Secondary: proportion of patients with sPGA (0), PASI90, PASI100, change in DLQI, improvement in itching based on NRS	Primary: PASI75 and sPGA (0,1) responses at week 12 were achieved by a significantly higher proportion of the ixekizumab-treated patients. Response rates associated with 80 mg every two weeks were numerically superior to those associated with 80 mg every four weeks. The proportion of patients with PASI75 response was 89.7% for the 80 mg every two weeks and 77.5% for the 80 mg every four weeks compared to 41.6% for etanercept (P<0.0001). The proportion of patients with sPGA (0,1) was 83.2% for the 80 mg every two weeks and 72.9% for the 80 mg every four weeks compared to 36.0% for etanercept (P<0.0001). For week 12 responders to ixekizumab, efficacy in terms of PASI 75 and sPGA (0,1) was maintained through the 60-week maintenance period compared to placebo (P values not reported). Secondary: There was a significantly greater improvement in secondary endpoints with ixekizumab compared to etanercept. Response rates associated with 80 mg every two weeks were numerically superior to those associated with 80 mg every four weeks. A greater proportion of ixekizumab-treated patients had sPGA (0) response compared to etanercept at 41.9% and 32.3% to 5.9% (P<0.0001). The percentage of patients with PASI90 was 70.7% and 59.7% for the ixekizumab-treated patients compared to 18.7% for etanercept (P<0.0001). Additionally, the percentage of patients with PASI100 was 40.5% and 30.8% for the ixekizumab-treated patients compared to 5.3% for etanercept (P<0.0001). Patients in both ixekizumab groups reported significant improvements in DLQI, NAPSI and itching by week 12 compared to etanercept groups (P<0.0001 for all endpoints).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo SQ every four weeks				
Griffiths et al.[62,63] (2015) UNCOVER-3 Induction phase ixekizumab 80 mg SQ every two weeks vs ixekizumab 80 mg SQ every four weeks vs etanercept 50 mg SQ twice weekly vs placebo SQ every two weeks Maintenance phase ixekizumab 80 mg SQ every four weeks	DB, MC, PC, RCT Patients ≥ 18 years of age with a minimum BSA involvement of 10%, PASI score of ≥12, sPGA ≥3 and candidates for phototherapy or systemic therapy	N= 1,346 12 weeks	Primary: PASI75 response, sPGA (0,1) with ≥2-point improvement from baseline Secondary: proportion of patients with sPGA (0), PASI90, PASI100, change in DLQI, change in NAPSI, improvement in itching based on NRS	Primary: PASI75 and sPGA (0,1) responses at week 12 were achieved by a significantly higher proportion of the ixekizumab-treated patients. Response rates associated with 80 mg every two weeks were numerically superior to those associated with 80 mg every four weeks. The proportion of patients with PASI75 response was 87.3% for the 80 mg every two weeks and 84.2% for the 80 mg every four weeks compared to 53.4% for etanercept (P<0.0001). The proportion of patients with sPGA (0,1) was 80.5% for the 80 mg every two weeks and 75.4% for the 80 mg every four weeks compared to 41.6% for etanercept (P<0.0001). Secondary: There was a significantly greater improvement in secondary endpoints with ixekizumab compared to etanercept. Response rates associated with 80 mg every two weeks were numerically superior to those associated with 80 mg every four weeks. A greater proportion of ixekizumab-treated patients had sPGA (0) response compared to etanercept at 40.3% and 36.0% to 8.6% (P<0.0001). The percentage of patients with PASI90 was 68.1% and 65.3% for the ixekizumab-treated patients compared to 25.7% for etanercept (P<0.0001). Additionally, the percentage of patients with PASI100 was 37.7% and 35.0% for the ixekizumab-treated patients compared to 7.3% for etanercept (P<0.0001). Patients in both ixekizumab groups reported significant improvements in DLQI, NAPSI and itching by week 12 compared to etanercept groups (P<0.0001, P<0.001 and P<0.0001, respectively).
Blauvelt et al.[64,65] (2020) IXORA-R	DB, MC, PG, RCT Adults with moderate-	N=1,027 24 weeks	Primary: PASI100 at week 12	Primary: The primary end point PASI 100 at week 12 was met [215/520 ixekizumab (41%); 126/507 guselkumab (25%); P<0.001].

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ixekizumab vs guselkumab	to-severe plaque psoriasis, defined as static Physician's Global Assessment ≥ 3, PASI ≥ 12 and involved body surface area ≥ 10%		Secondary: Other levels of improved PASI and sPGA at different time points including PASI 100 at week 24	Secondary: All major secondary end points measured up to week 12 were met, including PASI 50 at week one and PASI 75 at week two. At week 24, ixekizumab was noninferior to guselkumab (50% vs 52%, difference -2.3%), with no statistically significant difference in PASI 100 (P=0.41). More patients receiving ixekizumab showed completely clear nails at week 24 (52% vs 31%, P=0.007). The median time to first PASI 50/75/90 and PASI 100 were 2 and 7.5 weeks shorter, respectively, for patients on ixekizumab vs. guselkumab (P<0.001).
Leonardi et al.[66] (2008) PHOENIX-1 Ustekinumab 45 mg vs ustekinumab 90 mg vs placebo Each group received a subcutaneous injection at week 0, 4, and then every 12 weeks thereafter.	DB, MC, PC, PG, RCT Patients ≥18 years of age with a diagnosis of plaque psoriasis for ≥6 months, candidates for phototherapy or systemic therapy, had a baseline PASI score 12 or higher, and had ≥10% BSA involvement	N=766 ≤76 weeks	Primary: Proportion of patients achieving PASI 75 at week 12 Secondary: Not reported	Primary: Significantly more patients in both the 45 and 90 mg ustekinumab groups achieved the primary endpoint of PASI 75 at week 12 than did those in the placebo group (difference in response rate, 63.9%; 95% CI, 57.8 to 70.1; P<0.0001 and 63.3%; 95% CI, 57.1 to 69.4; P<0.0001 for 45 and 90 mg vs placebo, respectively. The onset of efficacy was rapid, with higher proportions of ustekinumab-treated patients achieving at least 50% improvement from baseline in PASI 50 by week two (P=0.0008 for 45 mg and P=0.0005 for 90 mg vs placebo) and PASI 75 by week four (P<0.0001 for each comparison vs placebo). Maximum efficacy was observed at week 24 in the 45 and 90 mg groups (PASI 75 response, 76.1% in 45 mg group and 85.0% in 90 mg group). Among patients re-randomized at week 40, maintenance of PASI 75 was better in patients receiving maintenance therapy than in patients withdrawn from therapy through at least one year (P<0.0001), The median percentage improvement in PASI remained stable to at least week 76. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Papp et al.[67] (2008) PHOENIX-2 Ustekinumab 45 mg vs ustekinumab 90 mg vs placebo Each group received an injection at week 0, 4, and then every 12 weeks thereafter. Partial responders at week 28 were re-randomized to continue dosing every 12 weeks or escalate to dosing every 8 weeks.	DB, MC, PC, RCT Patients ≥18 years of age, with a diagnosis of plaque psoriasis for ≥6 months, were candidates for phototherapy or systemic therapy, had a baseline PASI score 12 or higher, and had ≥10% BSA involvement	N=1,230 ≤52 weeks	Primary: Proportion of PASI 75 responders at week 12 Secondary: Proportion of patients with a physician's global assessment score of cleared or minimal at week 12, change in dermatology life quality index, the number of visits with PASI 75 response between weeks 40 and 52	Primary: Significantly more patients in both ustekinumab groups achieved PASI 75 at week 12 than did patients in the placebo group (difference in response rate, 63.1%; 95% CI, 58.2 to 68.0; P<0.0001 and 72.0%; 95% CI, 67.5 to 76.5; P<0.0001 for 45 and 90 mg vs placebo, respectively). Secondary: A greater proportion of patients in each ustekinumab group achieved a physician's global assessment of psoriasis of cleared or minimal at week 12 than did those in the placebo group (difference in response rate, 63.1%; 95% CI, 58.1 to 68.1; P<0.0001 for 45 mg vs placebo and 68.6%; 95% CI, 63.9 to 73.4; P<0.0001 for 90 mg vs placebo). Median changes in dermatology life quality index were greater in the ustekinumab groups than in the placebo group (mean of differences vs placebo, -8.0; 95% CI, -8.0 to -7.0; P<0.0001 for 45 mg and -9.0; 95% CI, -9.0 to -8.0; P<0.0001 for 90 mg vs placebo). A total of 22.7% of patients in the 45 mg group and 15.8% of patients in the 90 mg group were partial responders at week 28. Compared to patients responding to dosing every 12 weeks, partial responders tended to have higher bodyweight, more marked or severe disease as measured by physician's global assessment, and a higher incidence of PsA. Among the re-randomized partial responders, dosing intensification did not result in greater efficacy compared to continuing treatment every 12 weeks, as assessed by the number of visits between weeks 40 and 52 (four visits) at which patients achieved PASI 75 response (mean, 1.75 visits in the every eight week group and 1.56 in the every 12 week group; P=0.468). There was a lack of response to intensified dosing in the individuals receiving 45 mg, both in terms of number of visits at

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				which patients achieved PASI 75 response (mean, 1.13 vs 1.54 visits; P=0.210), and in terms of PASI 75 rates over time. This is in contrast to patients receiving intensified 90 mg dosing, which resulted in a greater number of visits with PASI 75 response (mean, 2.63 vs 1.58 visits; P=0.014) and higher PASI 75 response rate (68.8% of patients with dosing every eight weeks vs 33.3% of patients with dosing every 12 weeks; difference in response rate, 35.4%; 95% CI, 12.7 to 58.1 at week 52 for dosing every eight weeks vs dosing every 12 weeks; P=0.004).
Blauvelt et al.[68] (2016) CLEAR Secukinumab 300 mg at baseline and weeks 1, 2, and 3, then every four weeks starting from week 4 vs ustekinumab 45 mg in those with baseline weight ≤100 kg and 90 mg in those with baseline weight >100 kg, given at baseline, week 4, and then every 12 weeks	DB, AC, RCT Patients ≥18 years of age with a diagnosis of moderate-to-severe plaque psoriasis for ≥ 6 months disease (PASI score ≥ 12 at baseline, IGA 2011 modified score ≥ 3, and BSA involvement ≥ 10%); and disease inadequately controlled by topical treatments, phototherapy or previous systemic therapy	N=675 52 weeks	Primary: Proportion of patients who achieved PASI90 at week 16 Secondary: PASI75/90/100, IGA mod 2011 0/1, patient-reported psoriasis-related symptoms or pain, itching, and scaling, improvement in HRQOL, and safety and tolerability	Primary: Treatment with secukinumab resulted in a significantly higher proportion of patients achieving PASI90 compared to ustekinumab at week 16 (79.0% vs 57.6%; P<0.0001). Secondary: Treatment with secukinumab resulted in a significantly higher proportion of patients achieving PASI90 compared to ustekinumab at week 52 (74.9% vs 60.6%; P=0.0001). PASI75/90/100 and IGA mod 2011 0/1 response rates were consistently higher with secukinumab than with ustekinumab at all visits over 52 weeks, with significantly differences seen between treatment groups starting at week 1 for PASI75, week 2 for PASI90, and IGA mod 2011 0/1, and week 4 for PASI100. Patient-reported psoriasis-related symptoms of pain, itching, or scaling all decreased from baseline to week 52 in both treatment groups, with greater improvements in patients treated with secukinumab than in those treated with ustekinumab at all assessed time points. The decreases in the mean percentages of patients reporting symptoms from baseline to week 52 for secukinumab and ustekinumab were 80.1% vs 58.8% for pain, 77.6% vs 68.3% for itching, and 82.6% vs 71.8% for scaling. Statistical significance was tested at weeks 16 and 52 and was met for secukinumab for all three symptoms. A significantly higher proportion of patients receiving

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				secukinumab achieved DLQI 0/1 than those receiving ustekinumab at all assessed time points through week 52, with 71.6% vs 59.2%, respectively, achieving DLQI 0/1 at week 52 (P=0.0008). Proportions of patients that experienced adverse events, that experienced serious adverse events, and that discontinued treatment because of adverse events were similar between the two treatment groups.
Strober et al.[69] (2016) Ustekinumab vs infliximab vs adalimumab vs etanercept	MC, RETRO, OS Patients 18 to 99 years of age from the Psoriasis Longitudinal Assessment and Registry with psoriasis initiating therapy with a biologic agent for the first time and not currently on other systemic therapy	N=2,541 12 months	Primary: Proportions of patients achieving PGA 0/1 and mean decrease in percentage of BSA at 6 and 12 months Secondary: Proportion of patients achieving DLQI 0/1	Primary: The proportions of patients achieving PGA 0/1 with ustekinumab, infliximab, adalimumab, and etanercept were 57.1%, 36.4%, 50.1%, and 50.6%, respectively, at 6 months, and 59.2%, 42.0%, 56.5%, and 57.6%, respectively, at 12 months. Adjusted logistic regression analyses showed that patients receiving infliximab (OR, 0.396; 95% CI, 0.255 to 0.617; P<0.0001), adalimumab (OR, 0.686; 95% CI, 0.547 to 0.861; P=0.0012), and etanercept (OR, 0.554; 95% CI, 0.400 to 0.765; P=0.0003) were less likely to achieve PGA 0/1 at 6 months compared to those receiving ustekinumab. Similar OR estimates were observed at 12 months, but only the comparison between infliximab and ustekinumab showed a statistically significant difference (OR, 0.449; 95% CI, 0.260 to 0.774; P=0.004). The mean decreases in percentage of BSA affected were -14.7, -17.4, -10.6, and -11.4, at 6 months, and -16.3, -17.6, -12.3, and -13.8 at 12 months, with ustekinumab, infliximab, adalimumab, and etanercept, respectively. Secondary: The mean improvements in DLQI score from baseline were 6.9, 6.5, 4.5, and 6.2 at 6 months, and 7.5, 6.9, 4.9, and 5.4 at 12 months, with ustekinumab, infliximab, adalimumab, and etanercept, respectively.
Gomez-Garcia et al.[70] (2016)	SR, MA	N=6,540 (27 RCTs)	Primary: Odds of achieving	Primary: All agents that were evaluated showed superior efficacy

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Infliximab 5 mg/kg at weeks 0, 2, and 6, then every 8 weeks vs etanercept 50 mg twice weekly for 12 weeks, then 25 mg twice weekly or 50 mg weekly vs adalimumab 80 mg at week 0, 40 mg at week 1, then 40 mg every 2 weeks vs ustekinumab 45 mg or 90 mg at weeks 0 and 4, then every 12 weeks vs secukinumab 300 mg at weeks 0, 1, 2, and 3, then every 4 weeks All agents evaluated were used as monotherapy.	RCTs were included if they were placebo-controlled or head-to-head trials of infliximab, etanercept, adalimumab, ustekinumab, or secukinumab at pre-specified dosing as monotherapy for the treatment of plaque psoriasis in adult patients.	10 to 16 weeks	PASI75/90 Secondary: Odds of adverse events	compared to placebo with respect to all efficacy outcomes. Secukinumab 300 mg every four weeks and infliximab 5 mg/kg every eight weeks were the most effective agents, according to PASI75 and PASI90 response rates. Based on SUCRA values for the five agents evaluated, treatment with secukinumab appeared to have the highest probability of achieving PASI75, whereas treatment with infliximab appeared to have the highest likelihood of achieving PASI90. Secondary: Based on SUCRA values for the five agents evaluated, treatment with infliximab appeared to have the highest probability of leading to at least one adverse event. Ustekinumab was the only agent that did not show an increased risk of adverse events compared to placebo, and also had a lower risk of discontinuation because of adverse events compared to placebo (OR, 0.14; 95% CI, 0.03 to 0.63; P-value not reported).
Griffiths et al.[71] (2010)	MC, PG, RCT Patients ≥18 years of	N=903 12 weeks	Primary: PASI 75 at week 12	Primary: A greater number of patients achieved PASI 75 in the ustekinumab 45 mg group (67.5%) and ustekinumab 90 mg group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Etanercept 50 mg twice weekly vs ustekinumab 45 mg at weeks 0 and 4 vs ustekinumab 90 mg at weeks 0 and 4 Patients without a response to etanercept at week 12, received ustekinumab 90 mg at weeks 16 and 20; patients without a response to ustekinumab at week 12 received one additional study dose at week 16.	age, with a diagnosis of plaque psoriasis for ≥6 months, were candidates for phototherapy or systemic therapy, had a baseline PASI score ≥12, had a score ≥3 on physician's global assessment, had ≥10% BSA involvement, and had inadequate response, intolerance, or contraindication to ≥1 conventional systemic agent (i.e., MTX, cyclosporine, or psoralen plus ultraviolet A) and no previous treatment with etanercept or ustekinumab		Secondary: Physician's global assessment score of 0 or 1, PASI 90, difference between PASI at week 12 and 12 weeks after retreatment	(73.8%) than in the etanercept group (56.8%; P=0.01 vs ustekinumab 45 mg; P<0.001 vs ustekinumab 90 mg). Secondary: A larger proportion of ustekinumab patients met criteria for cleared or minimal on a physician's global assessment (score of 0 or 1) compared to etanercept patients (65.1% on ustekinumab 45 mg and 70.6% on ustekinumab 90 mg vs 49.0% on etanercept; P<0.001 for each comparison vs etanercept). PASI 90 was achieved by 36.4% of ustekinumab 45 mg patients, 44.7% of ustekinumab 90 mg patients and 23.1% of etanercept patients (P<0.001, for each comparison vs etanercept). Of the patients that crossed over to ustekinumab from etanercept, 48.9% achieved a PASI 75, 23.4% achieved PASI 90, 40.4% achieved cleared or minimal on the physician's global assessment. Of patients that received retreatment with ustekinumab, 84.4% had a physician's global assessment score of 0 to 2. The most commonly occurring adverse event in the etanercept group was injection site erythema (14.7%) and was reported more often than in the two ustekinumab groups combined (0.7%). At least one serious adverse effect was reported in 1.9, 1.2 and 1.2% of patients in the ustekinumab 45 mg, 90 mg and etanercept groups, respectively.
Bagel et al.[72] (2021) CLARITY Secukinumab 300 mg at baseline; weeks 1, 2, 3 and 4 and then every 4 weeks thereafter until week 48	DB, MC, PG, RCT Adult patients with moderate to severe chronic plaque psoriasis, as defined by PASI ≥ 12, IGA mod 2011 score ≥ 3 and affected body surface area involvement ≥10%	N=1,102 52 weeks	Primary: Proportion of patients achieving PASI 90 and IGA mod 2011 0 or 1 response (co-primary endpoints) at week 12 Secondary:	Primary: Secukinumab 300 mg showed superiority over ustekinumab 45/90 mg in the achievement of PASI 75, PASI 90 and PASI 100, as well as IGA mod 2011 0/1 and IGA mod 0 responses at every time point from week 4 through 52. Secondary: At week 52, a greater proportion of patients receiving secukinumab 300 mg than those receiving ustekinumab 45/90 mg achieved PASI 75 (89.0% vs. 82.1%; OR, 1.74; 95% CI, 1.21 to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ustekinumab (45 mg for patients weighing ≤ 100 kg or 90 mg for patients weighing >100 kg) at baseline, week 4, and then every 12 weeks thereafter until week 40	with disease inadequately controlled by topical treatments, phototherapy and/or previous systemic therapy		Achievement of PASI 75, PASI 90, PASI 100, IGA mod 2011 0/1, IGA mod 2011 0 and Dermatology Life Quality Index (DLQI) responses of no effect (0/1) through week 52	2.50; P=0.0013), PASI 90 (73.2% vs. 59.8%; OR, 1.84; 95% CI, 1.41 to 2.41; P<0.0001) and PASI 100 (48.9% vs. 33.5%; OR, 1.92; 95% CI, 1.48 to 2.47; P<0.0001) responses. A greater proportion of patients receiving secukinumab 300 mg than those receiving ustekinumab 45/90 mg also achieved IGA mod 2011 0/1 (76.0% vs. 60.2%; OR, 2.12; 95% CI, 1.61 to 2.79; P<0.0001) and IGA mod 2011 0 (50.3% vs. 33.8%; OR, 2.00; 95% CI, 1.55 to 2.57; P<0.0001) responses.
Reich et al.[73] (2017) reSURFACE 1 and reSURFACE 2 tildrakizumab 200 mg vs tildrakizumab 100 mg vs placebo vs etanercept 50 mg	ACC, DB, PG, RCT Participants aged 18 years or older with moderate-to-severe chronic plaque psoriasis were randomised to tildrakizumab 200 mg, tildrakizumab 100 mg, or placebo (2:2:1), or to tildrakizumab 200 mg, tildrakizumab 100 mg, placebo, or etanercept 50 mg (2:2:1:2)	N=2,862 16 weeks	Primary: proportion of patients achieving PASI 75 and PGA response (score of 0 or 1 with ≥2 grade score reduction from baseline) at week 12. Secondary: Safety and adverse events	Primary: reSURFACE 1 ran from Dec 10, 2012, to Oct 28, 2015. reSURFACE 2 ran from Feb 12, 2013, to Sept 28, 2015. In reSURFACE 1, 772 patients were randomly assigned, 308 to tildrakizumab 200 mg, 309 to tildrakizumab 100 mg, and 155 to placebo. At week 12, 192 patients (62%) in the 200 mg group and 197 patients (64%) in the 100 mg group achieved PASI 75, compared with 9 patients (6%) in the placebo group (p<0.0001 for comparisons of both tildrakizumab groups vs placebo). 182 patients (59%) in the 200 mg group and 179 patients (58%) in the 100 mg group achieved PGA responses, compared with 11 patients (7%) in the placebo group (p<0...0001 for comparisons of both tildrakizumab groups vs placebo). In reSURFACE 2, 1090 patients were randomly assigned, 314 to tildrakizumab 200 mg, 307 to tildrakizumab 100 mg, 156 to placebo, and 313 to etanercept. At week 12, 206 patients (66%) in the 200 mg group, and 188 patients (61%) in the 100 mg group achieved PASI 75, compared with 9 patients (6%) in the placebo group and 151 patients (48%) in the etanercept group (p<0.0001 for comparisons of both tildrakizumab groups vs placebo; p<0.0001 for 200 mg vs etanercept and p=0.0010 for 100 mg vs etanercept). 186 patients (59%) in the 200 mg group, and 168 patients (59%) [corrected] in the 100 mg group achieved a PGA response, compared with 7 patients (4%) in the placebo group and 149 patients (48%) in the etanercept group (p<0.0001 for comparisons of both tildrakizumab groups vs placebo; p=0.0031 for 200 mg vs etanercept and p=0.0663 for 100 mg vs etanercept).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Serious adverse events were similar and low in all groups in both trials. One patient died in reSURFACE 2, in the tildrakizumab 100 mg group; the patient had alcoholic cardiomyopathy and steatohepatitis, and adjudication was unable to determine the cause of death.
Lebwohl et al.[74] (2015) AMAGINE-2 and AMAGINE-3 Brodalumab 210 mg every 2 weeks vs Brodalumab 140 mg every 2 weeks vs ustekinumab 45 mg or 90 mg vs placebo	ACC, DB, PC, RCT Patients with moderate-to severe psoriasis were randomly assigned to receive brodalumab (210 mg or 140 mg every 2 weeks), ustekinumab (45 mg for patients with a body weight ≤100 kg and 90 mg for patients >100 kg), or placebo.	N=3,712 52 weeks	Primary: evaluate the superiority of brodalumab over placebo at week 12, as well as the superiority of brodalumab over ustekinumab at week 12, and sPGA score of 0 or 1 among the four brodalumab maintenance regimens at week 52. Secondary: Safety and adverse events:	Primary: At week 12, the PASI 75 response rates were higher with brodalumab at the 210-mg and 140-mg doses than with placebo (86% and 67%, respectively, vs. 8% [AMAGINE-2] and 85% and 69%, respectively, vs. 6% [AMAGINE-3]; P<0.001); the rates of sPGA scores of 0 or 1 were also higher with brodalumab (P<0.001). The week 12 PASI 100 response rates were significantly higher with 210 mg of brodalumab than with ustekinumab (44% vs. 22% [AMAGINE-2] and 37% vs. 19% [AMAGINE-3], P<0.001). The PASI 100 response rates with 140 mg of brodalumab were 26% in AMAGINE-2 (P=0.08 for the comparison with ustekinumab) and 27% in AMAGINE-3 (P=0.007). The proportion of patients with an sPGA score of 0 or 1 at week 52 was significantly higher among those who had received 210 mg or 140 mg of brodalumab every 2 weeks than among those who had received the other brodalumab maintenance regimens (P<0.001). The PASI response-over-time curves for patients who received brodalumab at a dose of 210 mg throughout the study or ustekinumab throughout the study showed that response rates increased through week 12 and stabilized during weeks 16 through 52. Secondary: Rates of neutropenia were higher with brodalumab and with ustekinumab than with placebo. Mild or moderate candida infections were more frequent with brodalumab than with ustekinumab or placebo. Through week 52, the rates of serious infectious episodes were 1.0 (AMAGINE-2) and 1.3 (AMAGINE-3) per 100 patient-years of exposure to brodalumab.
Armstrong et al.[75]	ACC, DB, PC, RCT	N=666	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2022) POETYK PSO-1 deucravacitinib 6 mg daily vs placebo vs apremilast 30 mg twice daily	Participants were randomized 2:1:1 to deucravacitinib 6 mg every day (n = 332), placebo (n = 166), or apremilast 30 mg twice a day (n = 168)	52 Weeks	response rates for ≥75% reduction from baseline in Psoriasis Area and Severity Index (PASI 75) and static Physician's Global Assessment score of 0 or 1 (sPGA 0/1) with deucravacitinib versus placebo at week 16 Secondary: sPGA 0 (clear), ≥ 90% and 100% reductions from baseline in PASI (PASI 90 and PASI 100), scalp-specific Physician's Global Assessment score of 0 or 1 (ss-PGA 0/1) (clear or almost clear), and Physician's Global Assessment of Fingernails score of 0 or 1 (PGA-F 0/1) (clear or almost clear)	At week 16, response rates were significantly higher with deucravacitinib versus placebo or apremilast for PASI 75 (194 [58.4%] vs 21 [12.7%] vs 59 [35.1%]; P<0.0001) and sPGA 0/1 (178 [53.6%] vs 12 [7.2%] vs 54 [32.1%]; P<0.0001). Efficacy improved beyond week 16 and was maintained through week 52. Adverse event rates with deucravacitinib were similar to those with placebo and apremilast. Secondary: A greater percentage of patients treated with deucravacitinib achieved PASI 90 versus patients in the placebo and apremilast groups at week 16 (35.5% vs 4.2% and 19.6%, respectively; P<0.0001 vs placebo; P=0.0002 vs apremilast) and versus the apremilast group at week 24 (42.2% vs 22.0%; P<0.0001). Statistical significance was also achieved for deucravacitinib versus placebo and apremilast on measures of complete skin clearance, including sPGA 0 (17.5% vs 0.6% and 4.8%; P<0.0001 for both) and PASI 100 (14.2% vs 0.6% and 3.0%; P<0.0001 for both) at week 16. In patients with moderate to severe scalp psoriasis (ss-PGA ≥3) at baseline (deucravacitinib, n = 209; placebo, n = 121; apremilast, n = 110), 70.3% treated with deucravacitinib achieved ss-PGA 0/1 at week 16 versus 17.4% and 39.1% of patients treated with placebo and apremilast, respectively (P<0.0001 for both). In the few patients with moderate to severe fingernail psoriasis (PGA-F ≥3) at baseline (deucravacitinib, n = 43; placebo, n = 34), response rates for PGA-F 0/1 at week 16 were numerically higher with deucravacitinib (20.9%) than with placebo (8.8%).
Bachelez et al.[76] (2021) Spesolimab 900 mg vs	DB, PC RCT patients with a GPP flare were randomly assigned in a 2:1 ratio to receive a single 900-	N=53 12 weeks	Primary: Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) pustulation subscore of 0 (range,	At baseline, 46% of the patients in the spesolimab group and 39% of those in the placebo group had a GPPGA pustulation subscore of 3, and 37% and 33%, respectively, had a pustulation subscore of 4. At the end of week 1, a total of 19 of 35 patients (54%) in the spesolimab group had a pustulation subscore of 0, as compared with 1 of 18 patients (6%) in the placebo group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	mg intravenous dose of spesolimab or placebo		0 [no visible pustules] to 4 [severe pustulation]) at the end of week 1 Secondary: GPPGA total score of 0 or 1 (clear or almost clear skin) at the end of week 1; scores range from 0 to 4, with higher scores indicating greater disease severity.	(difference, 49 percentage points; 95% confidence interval [CI], 21 to 67; P<0.001). A total of 15 of 35 patients (43%) had a GPPGA total score of 0 or 1, as compared with 2 of 18 patients (11%) in the placebo group (difference, 32 percentage points; 95% CI, 2 to 53; P = 0.02). Drug reactions were reported in 2 patients who received spesolimab, in 1 of them concurrently with a drug-induced hepatic injury. Among patients assigned to the spesolimab group, infections occurred in 6 of 35 (17%) through the first week; among patients who received spesolimab at any time in the trial, infections had occurred in 24 of 51 (47%) at week 12. Antidrug antibodies were detected in 23 of 50 patients (46%) who received at least one dose of spesolimab.
Reich et al.[77] (2019) IMMvent 150 mg risankizumab subcutaneously at weeks 0 and 4 or 80 mg adalimumab subcutaneously at randomisation, then 40 mg at weeks 1, 3, 5, and every other week thereafter during a 16-week double-blind treatment period (part A). For weeks 16-44 (part B), adalimumab intermediate responders were re-randomised 1:1 to continue 40 mg adalimumab or switch to 150 mg risankizumab	AC, DB, MC, RCT Adults with moderate-to-severe chronic plaque psoriasis	N=605 60 weeks	Primary: Induction: PASI90 and sPGA score of 0/1 at week 16; maintenance: PASI90 at week 44 Secondary: Safety	Primary: At week 16, PASI 90 was achieved in 218 (72%) of 301 patients given risankizumab and 144 (47%) of 304 patients given adalimumab (adjusted absolute difference, 24.9%; 95% CI, 17.5 to 32·4; P<0.0001), and sPGA scores of 0 or 1 were achieved in 252 (84%) patients given risankizumab and 252 (60%) patients given adalimumab (adjusted absolute difference, 23.3%; 95% CI, 16.6 to 30.1; P<0.0001). In the maintenance phase, among adalimumab intermediate responders, PASI 90 was achieved by 35 (66%) of 53 patients switched to risankizumab and 12 (21%) of 56 patients continuing adalimumab (adjusted absolute difference 45.0% [28.9 to 61.1]; P<0.0001) at week 44. Secondary: Adverse events were reported in 168 (56%) of 301 patients given risankizumab and 179 (57%) of 304 patients given adalimumab in part A, and among adalimumab intermediate responders, adverse events were reported in 40 (75%) of 53 patients who switched to risankizumab and 37 (66%) of 56 patients who continued adalimumab in the maintenance phase.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Stein Gold et al.[78] (2023) IMMpulse Risankizumab subcutaneous (150 mg at weeks 0 and 4) vs apremilast oral (30 mg twice daily) At week 16, all patients treated with apremilast were re-randomized (1:1) to risankizumab or apremilast, stratified by week-16 PASI 75 response	MC, OL, RCT, efficacy assessor-blinded Adults with a diagnosis of moderate chronic plaque psoriasis (≥6 months) and who were candidates for systemic therapy	N=352 52 weeks	Primary: PASI90 and sPGA 0/1with a two-grade or better improvement from baseline at week 16; PASI 90 in PASI 75 nonresponders with apremilast at week 16 at week 52 Secondary: Safety	Primary: At week 16, PASI 90 was achieved by 55.9% (95% CI, 47.0 to 64.9) and 5.1% (95% CI, 2.3 to 8.0), and sPGA 0/1 by 75.4% (95% CI, 67.7 to 83.2) and 18.4% (95% CI, 13.4 to 23.3), respectively. In the maintenance phase, among PASI 75 nonresponders with apremilast at week 16, 83 switched to risankizumab and 78 continued apremilast. At week 52, 72.3% (95% CI, 62.7 to 81.9) who switched to risankizumab achieved PASI 90 vs. 2.6% (95% CI, 0.0 to 6.1) who continued apremilast. Secondary: The most frequent adverse events (reported in ≥5%) in risankizumab-treated patients were COVID-19 infection and nasopharyngitis. Diarrhoea, nausea and headache were most frequent among apremilast-treated patients.
Warren et al.[79] (2021) IMMerge Risankizumab 150 mg vs secukinumab 300 mg	MC, OL, RCT, efficacy assessor-blinded Adult patients with chronic, moderate-to-severe plaque psoriasis	N=327 52 weeks	Primary: PASI90 at week 16 and week 52 Secondary: PASI 100, static Physician's Global Assessment 0 or 1, and PASI 75	Primary: Risankizumab was noninferior to secukinumab in the proportion of patients achieving PASI 90 at week 16 [73.8% vs 65.6%; difference of 8.2%; 96.25% CI, -2.2 to 18.6; within the 12% noninferiority margin] and superior to secukinumab at week 52 (86.6% vs 57.1%; difference of 29.8%; 95% CI, 20.8 to 38.8; P<0.001), thus meeting both primary endpoints. Secondary: All secondary endpoints (PASI 100, static Physician's Global Assessment 0 or 1, and PASI 75) at week 52 demonstrated superiority for risankizumab vs secukinumab (P<0.001).
Psoriatic Arthritis				
Deodhar et al.[80]	DB, PC, RCT	N=381	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2020) Guselkumab 100 mg every 4 weeks vs Guselkumab 100 mg at weeks 0, 4, then every 8 weeks vs placebo	Adults with active psoriatic arthritis (at least three swollen and three tender joints; and C-reactive protein ≥0.3 mg/dL) despite standard therapies.	24 weeks	American College of Rheumatology 20% improvement (ACR20) at week 24 in all patients per assigned treatment group using non-responder imputation Secondary: Safety was assessed in all patients per treatment received	The primary endpoint was met: ACR20 at week 24 was achieved by significantly greater proportions of patients in the guselkumab every 4 weeks group (76 [59%] of 128 [95% CI 50 to 68]) and every 8 weeks group (66 [52%] of 127 [43 to 61]) than in the placebo group (28 [22%] of 126 [15 to 30]), with percentage differences versus placebo of 37% (95% CI 26 to 48) for the every 4 weeks group and 30% (19 to 41) for the every 8 weeks group (both P<0.0001). Secondary: Serious adverse events up to week 24 occurred in no patients receiving guselkumab every 4 weeks, four (3%) patients receiving guselkumab every 8 weeks, and five (4%) patients receiving placebo. Up to week 24, one patient in the placebo group died from cardiac failure and two had serious infections; no guselkumab-treated patient died or had serious infections.
Chandran et al.[81] (2020) SPIRIT-P1 Ixekizumab 80 mg every 2 weeks (IXEQ2W) or every 4 weeks (IXEQ4W) after an initial dose of 160 mg vs adalimumab 40 mg every 2 weeks (ADA; active reference) vs placebo	MC, RCT Adults with active psoriatic arthritis who were naïve to biologic DMARDs	N=386 3 years double-blind (weeks 0 to 24), extension (weeks 24 to 52) and long-term extension (weeks 52 to 156)	Primary: Safety Secondary: Efficacy as determined by ACR and additional indexes	Primary: By week 156, 88% of IXEQ2W- and 87% of IXEQ4W-treated patients had experienced at least one treatment-emergent adverse event. The most frequent treatment-emergent adverse events were upper respiratory tract infection, injection site reaction, bronchitis and injection-site erythema. The majority of events were mild or moderate in severity (investigator assessed). Secondary: With IXEQ2W and IXEQ4W, respectively, the response rates persisted to week 156 as measured by the ACR response ≥20% (62.5 and 69.8%), ≥50% (56.1 and 51.8%) and ≥70% (43.8 and 33.4%), PASI 75 (69.1 and 63.5%), PASI 90 (64.5 and 51.2%) and PASI 100 (60.5 and 43.6%). Inhibition of radiographic progression also persisted to week 156 in 61% of IXEQ2W and 71% of IXEQ4W patients.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
At week 24 (week 16 for inadequate responders), ADA (after 8-week washout) and placebo patients were re-randomized to IXEQ2W or IXEQ4W				
Mease et al.[82] (2020) SPIRIT-H2H Ixekizumab (IXE) vs adalimumab (ADA)	MC, OL, PG, RCT Biological DMARD-naïve patients with both active psoriatic arthritis and skin disease and inadequate response to conventional synthetic disease-modifying antirheumatic drug (csDMARDs)	N=566 24 weeks	Primary: Both ACR50 and PASI100 superiority at week 24 Secondary: IXE non-inferior to ADA for achievement of ACR50 and superior to ADA for PASI100 response at week 24	Primary: The primary efficacy endpoint was met (IXE: 36%, ADA: 28%; p=0.036). Secondary: IXE was non-inferior for ACR50 response (IXE: 51%, ADA: 47%; treatment difference: 3.9%) and superior for PASI100 response (IXE: 60%, ADA: 47%; p=0.001). IXE had greater response versus ADA in additional PsA, skin, nail, treat-to-target and quality-of-life outcomes.
Smolen et al.[83] (2020) SPIRIT-H2H Ixekizumab (IXE) vs adalimumab (ADA)	MC, OL, PG, RCT Biological DMARD-naïve patients with both active psoriatic arthritis and skin disease and inadequate response to conventional synthetic disease-modifying antirheumatic drug (csDMARDs)	N=566 52 weeks	Primary: Both ACR50 and PASI100 superiority at week 52 Secondary: Musculoskeletal, psoriasis, quality-of life outcomes, subgroup analyses and safety	Primary: Overall, 246 (87%) patients treated with IXE and 237 (84%) treated with ADA completed the week 52 study visit. A higher proportion of patients treated with IXE achieved simultaneous ACR50 and PASI100 versus ADA (39.2% vs 26.1%; P<0.001). Secondary: IXE and ADA treatment resulted in similar response rates for ACR50 (49.8% vs 49.8%), ACR20 (69.6% vs 68.9%) and ACR70 (35.3% vs 34.3%) at week 52. The proportion of patients achieving Minimal Disease Activity, Very Low Disease Activity, Disease Activity in PSoriatic Arthritis remission and Disease Activity in PSoriatic Arthritis low disease activity or remission was not significantly different between IXE and ADA at week 52. here were no new safety findings for IXE or ADA.
Kristensen et al.[84] (2023) KEEPsAKE 1	DB/OL, PC, RCT Patients with active	N=964 52 weeks	Primary: ACR outcomes	Primary: At week 24 (period 1), greater proportions of patients receiving risankizumab achieved the primary end point of ACR20

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Risankizumab subcutaneous 150 mg at weeks 0, 4 and 16 vs placebo At week 24 (period 2), all continuing patients received OL risankizumab 150 mg every 12 weeks through week 208.	PsA who had previous inadequate response/intolerance to one or more conventional synthetic DMARDs		Secondary: Safety	compared with patients receiving placebo (Non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 (NRI-C), 57.3% vs 33.5%; P<0.001). In patients randomized to receive continuous risankizumab treatment (period 1 and 2), the proportion of patients achieving ACR20 response increased from week 24 (57.3%) to week 52 (70.0%). Similarly, for ACR50 and ACR70, there were significant differences between risankizumab and placebo at week 24 (P<0.001). In patients randomized to receive continuous risankizumab treatment, the ACR50 response rate increased from 33.4% at week 24 to 43.3% at week 52, and the ACR70 response rate increased from 15.3% to 25.9%. Similar result trends were observed for other efficacy measures. Secondary: Risankizumab was well tolerated through 52 weeks of treatment with a consistent safety profile from week 24 through week 52.
Östör et al.[85] (2023) KEEPsAKE 2 Risankizumab subcutaneous 150 mg at weeks 0, 4 and 16 vs placebo At week 24 (period 2), all continuing patients received OL risankizumab 150 mg every 12 weeks through week 208.	DB/OL, PC, RCT Patients with active PsA who had previous inadequate response/intolerance to one or two biologic therapies or one or more conventional synthetic DMARDs	N=443 52 weeks	Primary: ACR outcomes Secondary: Safety	Primary: A greater proportion of patients receiving risankizumab achieved the primary endpoint of ACR20 (51.3% vs 26.5%, P<0.001) and all secondary endpoints were met (P<0.05) compared with placebo at week 24. In patients randomized to receive continuous risankizumab, the proportion achieving ACR20 increased from week 24 (51.3% [115/224]) to week 52 (58.5% [131/224]). Similarly, the proportion of patients achieving ACR50 and ACR70 increased from week 24 (26.3% [59/224] and 12.0% [27/224]) to week 52 (32.1% [72/224] and 16.5% [37/224]). Similar trends were observed for other efficacy measures. Secondary: Rates of serious treatment-emergent adverse events (TEAEs) and TEAEs leading to discontinuation remained stable through week 52, and no deaths were reported.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
McInnes et al.[86] (2013) PSUMMIT 1 Ustekinumab 45 mg at weeks 0, 4, and every 12 weeks vs ustekinumab 90 mg at weeks 0, 4, and every 12 weeks vs placebo Patients receiving placebo were switched to ustekinumab 45 mg at week 16 (if they did not have an improvement of at least 5% in tender and swollen joints) or at week 24 (if they had an improvement at week 16). Patients receiving ustekinumab 45 mg were switched to ustekinumab 90 mg if they did not have an improvement of at least 5% in tender and swollen joints at week 16.	DB, MC, PC, RCT Patients ≥18 years of age with active PsA for ≥6 months despite treatment with DMARDs for ≥3 months or NSAIDs for ≥4 weeks, or both, or with intolerance to these treatments	N=615 52 weeks	Primary: ACR 20 response at week 24 Secondary: ACR 50, ACR 70, HAQ-DI, and PASI 75 at week 24	Primary: A greater proportion of patients treated with ustekinumab 45 mg (42.4%) and ustekinumab 90 mg (49.5%) achieved an ACR 20 response at week 24 compared to placebo (22.8%; P<0.0001 for both comparisons). Secondary: A greater proportion of patients treated with ustekinumab 45 mg (24.9%) and ustekinumab 90 mg (27.9%) achieved an ACR 50 response at week 24 compared to placebo (8.7%; P<0.0001 for both comparisons). A greater proportion of patients treated with ustekinumab 45 mg (12.2%) and ustekinumab 90 mg (14.2%) achieved an ACR 70 response at week 24 compared to placebo (2.4%; P=0.0001 and P<0.0001, respectively). At week 24, improvements in HAQ-DI scores from baseline were greater in patients treated with ustekinumab 45 mg (median change -0.25) and ustekinumab 90 mg (median change -0.25) compared to placebo (median change 0; P<0.0001 for both comparisons). A greater proportion of patients treated with ustekinumab 45 mg (57.2%) and ustekinumab 90 mg (62.4%) achieved PASI 75 at week 24 compared to placebo (11.0%; P<0.0001 for both comparisons).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
The use of a DMARD or an NSAID was allowed if the dose was stable for three months and four weeks before the start of the study, respectively.				

*Not currently available in the United States.
Study abbreviations: CI=confidence interval, DB=double-blind, DD=double dummy, ES=extension study, HR=hazard ratio, IR=incidence rate, MA=meta-analysis, MC=multicenter, NNH=number needed to harm, NNT=number needed to treat, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel group, PRO=prospective, R=randomized, RCT=randomized controlled trial, RD=risk difference, RR=relative risk, SD=standard deviation, SR=systematic review, WMD=weighted mean difference
Miscellaneous abbreviations: ACR=American College of Rheumatology, ACR-N=numeric index of the ACR response, ACR pedi 30=American College of Rheumatology pediatric 30% improvement criteria, ALT=alanine transaminase, AS=ankylosing spondylitis, ASDAS=ankylosing spondylitis disease activity score, ASAS=Assessment of Spondyloarthritis International Society criteria, AST=aspartate aminotransferase, AUC=area under the curve, BASDAI=Bath Ankylosing Spondylitis Disease Activity Index, BASFI=Bath Ankylosing Spondylitis Functional Index, BASMI=Bath Ankylosing Spondylitis Metrology Index, BSA=body surface area, CCP=cyclic citrullinated protein CD=Crohn's disease, CDAI=Crohn's disease activity index, CDAI-100=Crohn's disease activity index decrease of ≥100 points from baseline, CHAQ=Childhood Health Assessment Questionnaire, CNS=central nervous system, COX=cyclooxygenase, CR-70=clinical remission, CR-100=clinical remission 100, CRP=C-reactive protein, CSF=cerebrospinal fluid, CT=computed tomography, DAS 28=Disease Activity Score in 28 joints, DLQI=Dermatology Life Quality Index, DMARD=disease-modifying antirheumatic drug, DOI=definition of improvement, ECL=electrogenerated chemiluminescence, EIM=extra-intestinal manifestations, ELISA=enzyme-linked immunosorbent assay, ESR=erythrocyte sedimentation rate, EULAR=European League Against Rheumatism Response criteria, FACIT-F=Functional Assessment of Chronic Illness Therapy-Fatigue, HAQ=health assessment questionnaire, HAQ-DI=health assessment questionnaire–disability index, HBI=Harvey-Bradshaw index, HCQ=hydroxychloroquine, HDL=high density lipoprotein, IBDQ=inflammatory bowel disease questionnaire, IOIBD=international organization for the study of inflammatory bowel disease, ITT=intent to treat, JIA=juvenile idiopathic arthritis, JRA=juvenile rheumatoid arthritis, JSN=joint space narrowing, LDL=low density lipoprotein, MCR=major clinical response, MRE=magnetic resonance enterography, MRI=magnetic resonance imaging, mTSS=modified Total Sharp Scores, MTX=methotrexate, NOMID=neonatal-onset multisystem inflammatory disease, nr-axSpA= non-radiographic-axial spondyloarthritis, NSAIDs=nonsteroidal anti-inflammatory drugs, PASI=psoriasis area and severity index, PCDAI=pediatric Crohn's disease activity index, PGA=physician global assessment, PsA=psoriatic arthritis, PsARC=psoriatic arthritis response criteria, PSSI=psoriasis scalp severity index, SIAQ=Self-Injection Assessment Questionnaire, RA=rheumatic arthritis, RF=rheumatoid factor, SF-36=short form-36, SF-36 MCS=short form-36-mental component, SF-36 PCS=short form-36-physical component, SAA=serum amyloid A, SHS=Sharp van der Heijde Score, SMD=standardized mean differences, SSZ=sulfasalazine, TB=tuberculosis, TNF=tumor necrosis factor, VAS=visual analog scale

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX.Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 10. Relative Cost of the Skin and Mucus Membrane Immunomodulators

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Bimekizumab-bkzx	injection	Bimzelx®	$$$$$	N/A
Brodalumab	injection	Siliq®	$$$$$	N/A
Deucravacitinib	tablet	Sotyktu®	$$$$$	N/A
Dupilumab	injection	Dupixent®	$$$$$	N/A
Guselkumab	injection	Tremfya®	$$$$$	N/A
Ixekizumab	injection	Taltz®	$$$$$	N/A
Risankizumab-rzaa	injection	Skyrizi®	$$$$$	N/A
Spesolimab-sbzo	injection	Spevigo®	$$$$$	N/A
Tildrakizumab-asmn	injection	Ilumya®	$$$$$	N/A
Tralokinumab-ldrm	injection	Adbry®	$$$$$	N/A
Ustekinumab	injection	Stelara®	$$$$$	N/A

*Generic is available in at least one dosage form or strength.
N/A=Not available

X.Conclusions

The skin and mucus membrane immunomodulators are used for a variety of inflammatory and immunologic conditions.[1-13] Many of the drugs in this class have overlapping indications and uses across other classification categories (i.e., AHFS designations), including the disease-modifying antirheumatic drugs and other immunomodulatory classifications.

Current clinical guidelines support the use of the skin and mucus membrane immunomodulators with respect to their FDA-approved indications, particularly in conditions where patients were unresponsive or refractory to traditional treatments, which usually include nonsteroidal anti-inflammatory drugs (NSAIDs) and/or methotrexate depending on the disease state.[15-28] Most of the agents in this class are indicated for the treatment of psoriasis. For moderate to severe plaque psoriasis, a systemic agent is recommended for patients who have failed or have a contraindication to phototherapy. Systemic agents include retinoids, methotrexate, cyclosporine, apremilast (Otezla®), biologic immune modifying agents, and deucravacitinib (Sotyktu®). Treatment choice for any of the disease states treated with these agents should be driven by disease severity, shared decision making, and the presence of any comorbid conditions. In general, no one immune modulating agent is preferred over another, and guideline recommendations are in-line with the approved labeling.[15-28] Certain disease state guidelines recommend use of specific classes of drugs before switching to others (i.e., TNF inhibitor before switching to an IL-17 inhibitor or JAK inhibitor).

Most research with these agents is in comparison to placebo, with the skin and mucus membrane immunomodulators demonstrating greater symptomatic impovement.[34-86] There are various head-to-head trials for these agents, mainly for the treatment of moderate to severe plaque psoriasis. The evidence suggests that some products may be utilized over others for certain patient populations and indications.[59,61-63,68,72-74,87-90] The guidelines do not recommend one agent over another; however, if the guidelines are updated they should be re-reviewed at that time.[21]

Brodalumab is available only through a Risk Evaluation and Mitigation Strategy (REMS) Program due to the risk of suicidal ideation and behavior as outlined in the boxed warning within the prescribing information.[3]

There is insufficient evidence to support that one brand skin and mucus membrane immunomodulator is safer or more efficacious than another within its FDA-approved indication(s). The drugs in this AHFS class are used in a specific patient population. Because these agents have narrow indications with limited usage and serious adverse events, these agents should be managed through the medical justification portion of the prior authorization process.

Therefore, all skin and mucus membrane immunomodulators within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI.Recommendations

No brand skin and mucus membrane immunomodulator is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Taltz® [package insert]. Indianapolis (IN): Eli Lilly, LLC.; 2021 Mar.
2. Ilumya® [package insert]. Cranbury (NJ): Sun Pharmaceutical Industries, Inc.; 2020 Jul.
3. Siliq® [package insert] Bridgewater (NJ): Bausch Health US, LLC.; 2020 Apr.
4. Skyrizi® [package insert]. North Chicago (IL): AbbVie Inc.; 2022 Jun.
5. Spevigo® [package insert]. Ridgefield (CT): Boehringer Ingelheim Pharmaceuticals, Inc.; 2022 Jun.
6. Stelara® [package insert]. Horsham (PA): Janssen Biotech, Inc.; 2020 Dec.
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