Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Clinical Packet
November 8, 2017

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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. For a non-preferred product to be approved, failure with a designated number of preferred agents and clinical criteria must be met.

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 in 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:

Maximum Unit Limitations
Early Refill
Brand Limit Switchover
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-9 code(s) may be used. Use of ICD-9 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 provided through a government or state sponsored drug assistance program for uninsured patients may be counted toward the stable therapy requirement. 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 different subclasses, prior therapies must include at least 2 prescribed and preferred agents from either or both 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 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 (PA)

- Antihypertensive agents are included in the electronic PA program.

Verbal PA Requests

- Not Applicable

Anti-infective Agents

Preferred Agents

- Requests for preferred agents in the HCV anti-infective class must meet certain clinical criteria, please see Form 415 Criteria instruction booklet.

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 two treatment trials of no less than three-days each, with at least two prescribed and preferred anti-infectives, either generic, OTC, or brand, for the above diagnosis within the past 30 days or have a documented allergy or contraindication to all preferred agents for the diagnosis submitted.

- For the HCV anti-infectives, please see separate PA forms for specific information.

Stable Therapy

- Patients on anti-infective therapy while institutionalized once discharged or transferred to another setting or patients having a 60 day consecutive stable therapy may continue on that therapy with supportive medical justification or documentation.

Medical Justification

- Medical justification may include peer-reviewed literature, medical record documentation, or other information specifically requested. Approval may also be given, with medical justification, if the medication requested is indicated for first line therapy when there are no other indicated preferred agents available or if indicated by susceptibility testing or evidence of resistance to all preferred agents.

PA Approval Timeframes

- Approval may be given for up to 12 months.

Electronic Prior Authorization (EPA)

- Not Applicable.

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

November 8, 2017
9:00 a.m. – 12:00 p.m.

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1. Opening remarks……..……..……Chair
2. Approval of August 9, 2017 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……...University of Massachusetts 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
   - HCV Antivirals – AHFS 081840
6. Results of voting announced……..…….....……..……...……..Chair
7. New business
   - Election of Committee's Chairperson and Vice Chairperson
8. Next meeting date
   - January 17, 2018
   - May 9, 2018
   - August 8, 2018
   - November 7, 2018
9. Adjourn

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Central Alpha-Agonists
AHFS Class 240816
November 8, 2017

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.[3,4] 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).[5] 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.[3,6-12] 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.[6-12]

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 August 2015.

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	tablet, transdermal patch	Catapres®*, Catapres-TTS®*	clonidine, Catapres-TTS®*
Guanfacine	tablet	N/A	guanfacine
Methyldopa	tablet	N/A	methyldopa
Methyldopate	injection^	N/A	methyldopate
Combination Products			
Methyldopa and hydrochlorothiazide	tablet	N/A	methyldopa 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 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.
American Society of Hypertension/ International Society of Hypertension: **Clinical Practice Guidelines for the Management of Hypertension in the Community (2014)**[13]	Nonpharmacologic treatment • In patients with hypertension that is no more severe than stage one and is not associated with evidence of abnormal cardiovascular findings or other cardiovascular risks, six to 12 months of lifestyle changes can be attempted in the hope that they may be sufficiently effective to make it unnecessary to use medicines. • It may be prudent to start treatment with drugs sooner if it is clear that the blood pressure is not responding to the lifestyle methods or if other risk factors appear. • Weight loss: In patients who are overweight or obese, weight loss is helpful in treating hypertension, diabetes, and lipid disorders. • Salt reduction: Reduction of salt intake is recommended because it can reduce blood pressure and decrease the need for medications in patients who are "salt sensitive."

Clinical Guideline	Recommendations

	• Exercise: Regular aerobic exercise can help reduce blood pressure.
	• Alcohol consumption: Up to two drinks a day can be helpful in protecting against cardiovascular events, but greater amounts of alcohol can raise blood pressure and should therefore be discouraged. In women, alcohol should be limited to one drink a day.
	• Cigarette smoking: Stopping smoking will not reduce blood pressure, but since smoking by itself is such a major cardiovascular risk factor, patients must be strongly urged to discontinue this habit.
	
	<u>Drug treatment of hypertension</u>
	• Treatment with drugs should be started in patients with blood pressures >140/90 mm Hg in whom lifestyle treatments have not been effective.
	• In patients with stage two hypertension (blood pressure ≥160/100 mm Hg), drug treatment should be started immediately after diagnosis, usually with a two-drug combination, without waiting to see the effects of lifestyle changes.
	• For patients older than 80 years, the suggested threshold for starting treatment is at levels ≥150/90 mm Hg. Thus, the target of treatment should be <140/90 mm Hg for most patients but <150/90 mm Hg for older patients (unless these patients have chronic kidney disease or diabetes, when <140/90 mm Hg can be considered).
	• Most patients will require more than one drug to achieve control of their blood pressure.
	• In general, increase the dose of drugs or add new drugs at approximately two to three week intervals. This frequency can be faster or slower depending on the judgment of the practitioner. In general, the initial doses of drugs chosen should be at least half of the maximum dose so that only one dose adjustment is required thereafter. It is generally anticipated that most patients should reach an effective treatment regimen, whether one, two, or three drugs, within six to eight weeks.
	• Choice of drugs should be influenced by the age, ethnicity/race, and other clinical characteristics of the patient.
	• The choice of drugs will also be influenced by other conditions (e.g., diabetes and coronary disease) associated with the hypertension. Pregnancy also influences drug choice.
	• Long-acting drugs that need to be taken only once daily are preferred to shorter-acting drugs that require multiple doses because patients are more likely to follow a simple treatment regimen.
	• This guideline only makes recommendations for drug classes, not individual agents. There is an assumption, unless otherwise stated, that all drugs in a class are similar to each other.
	• Drug selectin when hypertension is the only or main concern:
	  ○ For black patients of all ages, use calcium channel blocker (CCB) or thiazide diuretic as first drug, then add angiotensin receptor blocker (ARB) or angiotensin-converting enzyme (ACE) inhibitor if needed.
	  ○ For white and other non-black patients <60 years of age, use ARB or ACE inhibitor as first drug, then add CCB or thiazide diuretic if needed.
	  ○ For white and other non-black patients ≥60 years of age, use CCB or thiazide diuretic as first drug, then add ARB or ACE inhibitor if needed.
	• Drug selection when hypertension is associated with other conditions:
	  ○ For patients with hypertension and diabetes, use ARB or ACE inhibitor as first drug (note, in black patients it is acceptable to start with a CCB or thiazide), then add CCB or thiazide diuretic (unless starting on CCB or thiazide in black patients) if needed.
	  ○ For patients with hypertension and chronic kidney disease, use ARB or ACE inhibitor as first drug, then add CCB or thiazide diuretic if needed.
	  ○ For patients with hypertension and clinical coronary artery disease, use β-

Clinical Guideline	Recommendations
	blocker plus ARB or ACE inhibitor as first drugs, then add CCB or thiazide diuretic if needed. ○ For patients with hypertension and stroke history, use ACE inhibitor or ARB as first drug, then add thiazide diuretic or CCB if needed. • For patients with hypertension and heart failure, patients with h symptomatic heart failure should usually receive an ARB or ACE inhibitor plus β-blocker plus diuretic plus spironolactone regardless of blood pressure. A dihydropyridine CCB can be added if needed for blood pressure control.
Hypertension Canada: **2017 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults (2017)**[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. <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>Guidelines for individuals 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.
	
	<u>Treatment of hypertension in association with stroke</u>
	• BP management in acute ischemic stroke (onset to 72 hours)
	  ○ For patients with ischemic stroke not eligible for thrombolytic therapy, treatment of hypertension in the setting of acute ischemic stroke or transient ischemic attack should not be routinely undertaken. Extreme BP increases (e.g., SBP >220 mmHg or DBP >120 mmHg) may be treated to reduce the BP by approximately 15%, and not more than 25%, over the first 24 hours with gradual reduction thereafter. Avoid excessive lowering of BP because this might exacerbate existing ischemia or might induce ischemia, particularly in the setting of intracranial arterial occlusion or extracranial carotid or vertebral artery occlusion. Pharmacological agents and routes of administration should be chosen to avoid precipitous decreases in BP.
	  ○ For patients with ischemic stroke eligible for thrombolytic therapy, very high BP (>185/110 mmHg) should be treated concurrently in patients receiving thrombolytic therapy for acute ischemic stroke to reduce the risk of secondary intracranial hemorrhage.
	• 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)
	  ○ For patients with intracerebral hemorrhage (ICH) in the hyperacute phase (in the first 24 hours) SBP lowering to <140 mmHg should be avoided because of an absence of benefit (relative to a target of <180 mmHg) and some suggestion of harm.
	
	<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>
	• For patients with nondiabetic chronic kidney disease, target BP is <140/90 mmHg.
	• For patients with hypertension and proteinuric chronic kidney disease (urinary protein >500 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.
	• Thiazide/thiazide-like diuretics are recommended as additive antihypertensive therapy. For patients with chronic kidney disease and volume overload, loop

Clinical Guideline	Recommendations
	diuretics are an alternative. • 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. • In patients with hypertension attributable to FMD-related renal artery stenosis, revascularization should be considered. • 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. Combination therapy using two first-line agents may also be considered as initial treatment of hypertension if SBP is 20 mmHg greater than target or if DBP is 10 mmHg greater than target. However, caution should be exercised in patients in whom a substantial decrease in BP is more likely or poorly tolerated (e.g., elderly patients and patients with autonomic neuropathy). • 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.
European Society of Hypertension/European Society of Cardiology: **2013 Guidelines for the management of arterial hypertension (2013)**[15]	The 2013 guidelines on hypertension of the European Society of Hypertension and the European Society of Cardiology follow the guidelines jointly issued by the two societies in 2003 and 2007. Treatment strategies and choice of antihypertensive drugs • Diuretics (including thiazides, chlorthalidone, and indapamide), β-blockers, calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) are all suitable for the initiation and maintenance of antihypertensive treatment, either as monotherapy or in some combinations. • Some agents should be considered as the preferential choice in specific conditions because used in trials in those conditions or because of greater effectiveness in specific types of organ damage.

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	• Initiation of antihypertensive therapy with a two-drug combination may be considered in patients with markedly high baseline blood pressure (BP) or at high cardiovascular (CV) risk. • The combination of two antagonists of the renin-angiotensin system (RAS) is not recommended and should be discouraged. • Other drug combinations should be considered and probably are beneficial in proportion to the extent of BP reduction. However, combinations that have been successfully used in trials may be preferable. • Combinations of two antihypertensive drugs at fixed doses in a single tablet may be recommended and favored, because reducing the number of daily pills improves adherence, which is low in patients with hypertension. <u>Treatment strategies in white-coat and masked hypertension</u> • In white-coat hypertensives without additional risk factors, therapeutic intervention may be limited to lifestyle changes only, but this decision should be accompanied by close follow-up. • In white-coat hypertensives with a higher CV risk because of metabolic derangements or asymptomatic organ damage, drug treatment may be considered in addition to lifestyle changes. • In masked hypertension, both lifestyle measures and antihypertensive drug treatment should be considered, because this type of hypertension has been consistently found to have a CV risk very close to that of in- and out-of-office hypertension. <u>Antihypertensive treatment strategies in the elderly</u> • In elderly hypertensives with SBP ≥160 mmHg there is solid evidence to recommend reducing SBP to between 150 and 140 mmHg. • In fit elderly patients <80 years old antihypertensive treatment may be considered at SBP values ≥140 mmHg with a target SBP <140 mmHg if treatment is well tolerated. • In individuals older than 80 years with an initial SBP ≥160 mmHg, it is recommended to reduce SBP to between 150 and 140 mmHg, provided they are in good physical and mental conditions. • In frail elderly patients, it is recommended to leave decisions on antihypertensive therapy to the treating physician, and based on monitoring of the clinical effects of treatment. • Continuation of well-tolerated antihypertensive treatment should be considered when a treated individual becomes an octogenarian. • All hypertensive agents are recommended and can be used in the elderly, although diuretics and calcium antagonists may be preferred in isolated systolic hypertension. <u>Treatment strategies in hypertensive women</u> • Hormone therapy and selective estrogen receptor modulators are not recommended and should not be used for primary or secondary prevention of CVD. • If treatment of younger perimenopausal women is considered for severe menopausal symptoms, the benefits should be weighed against potential risks. • Drug treatment of severe hypertension in pregnancy (SBP >160 mmHg or DBP >110 mmHg) is recommended. • Drug treatment may also be considered in pregnant women with persistent elevation of BP ≥150/95 mmHg, and in those with BP ≥140/90 mmHg in the presence of gestational hypertension, subclinical organ damage or symptoms. • In women at high risk of pre-eclampsia, provided they are at low risk of gastrointestinal hemorrhage, treatment with low dose aspirin from 12 weeks until

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	delivery may be considered. • In women with child-bearing potential RAS blockers are not recommended and should be avoided. • Methyldopa, labetalol, and nifedipine should be considered preferential antihypertensive drugs in pregnancy. Intravenous labetalol or infusion of nitroprusside should be considered in case of emergency (pre-eclampsia). <u>Treatment strategies in patients with diabetes</u> • While initiation of antihypertensive drug treatment in diabetic patients whose SBP is ≥160 mmHg is mandatory, it is strongly recommended to start drug treatment also when SBP is ≥140 mmHg. • A SBP goal <140 mmHg is recommended in patients with diabetes. • The DBP target in patients with diabetes is recommended to be <85 mmHg. • All classes of antihypertensive agents are recommended and can be used in patients with diabetes; RAS blockers may be preferred, especially in the presence of proteinuria or microalbuminuria. • It is recommended that individual drug choice takes comorbidities into account. • Simultaneous administration of two blockers of the RAS is not recommended and should be avoided in patients with diabetes <u>Treatment strategies in hypertensive patients with metabolic syndrome</u> • Lifestyle changes, particularly weight loss and physical exercise, are to be recommended to all individuals with the metabolic syndrome. These interventions improve not only BP, but the metabolic components of the syndrome and delay diabetes onset. • As the metabolic syndrome can be considered a 'pre-diabetic' state, antihypertensive agents potentially improving or at least not worsening insulin sensitivity, such as RAS blockers and calcium antagonists, should be considered as the preferred drugs. Beta-blockers (with the exception of vasodilating β-blockers) and diuretics should be considered only as additional drugs, preferably in association with a potassium-sparing agent. • It is recommended to prescribe antihypertensive drugs with particular care in hypertensive patients with metabolic disturbances when BP is ≥140/90 mmHg after a suitable period of lifestyle changes, and to maintain BP <140/90 mmHg. • BP lowering drugs are not recommended in individuals with metabolic syndrome and high normal BP. <u>Therapeutic strategies in hypertensive patients with nephropathy</u> • Lowering SBP to <140 mmHg should be considered. • When overt proteinuria is present, SBP values <130 mmHg may be considered, provided that changes in eGFR are monitored. • RAS blockers are more effective in reducing albuminuria than other antihypertensive agents, and are indicated in hypertensive patients in the presence of microalbuminuria or overt proteinuria. • Reaching BP goals usually requires combination therapy, and it is recommended to combine RAS blockers with other antihypertensive agents. • Combination of two RAS blockers, though potentially more effective in reducing proteinuria, is not recommended. • Aldosterone antagonists cannot be recommended in chronic kidney disease (CKD), especially in combination with a RAS blocker, because of the risk of excessive reduction in renal function and of hyperkalemia. <u>Therapeutic strategies in hypertensive patients with cerebrovascular disease</u> • It is not recommended to intervene with BP-lowering therapy during the first week after acute stroke irrespective of BP level, although clinical judgement

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	should be used in the face of very high SBP values. • Antihypertensive treatment is recommended in hypertensive patients with a history of stroke or transient ischemic attack (TIA), even when initial SBP is in the 140 to 159 mmHg range. • In hypertensive patients with a history of stroke or TIA, a SBP goal of <140 mmHg should be considered. • In elderly hypertensives with previous stroke or TIA, SBP values for intervention and goal may be considered to be somewhat higher. • All drug regimens are recommended for stroke prevention, provided that BP is effectively reduced. <u>Therapeutic strategies in hypertensive patients with heart disease</u> • In hypertensive patients with CHD, a SBP goal <140 mmHg should be considered. • In hypertensive patients with a recent myocardial infarction, β-blockers are recommended. In case of other CHD all antihypertensive agents can be used, but β-blockers and calcium antagonists are to be preferred for symptomatic reasons (angina). • Diuretics, β-blockers, ACE inhibitors, angiotensin receptor blockers, and/or mineralocorticoid receptor antagonists are recommended in patients with heart failure or severe left ventricular (LV) dysfunction to reduce mortality and hospitalization. • In patients with heart failure and preserved ejection fraction (EF), there is no evidence that antihypertensive therapy per se or any particular drug, is beneficial. However, in these patients, as well as in patients with hypertension and systolic dysfunction, lowering SBP to around 140 mmHg should be considered. Treatment guided by relief of symptoms (congestion with diuretics, high heart rate with β-blockers, etc.) should also be considered. • ACE inhibitors and angiotensin receptor blockers (and β-blockers and mineralocorticoid receptor antagonists if heart failure coexists) should be considered as antihypertensive agents in patients at risk of new or recurrent atrial fibrillation. • It is recommended that all patients with left ventricular hypertrophy (LVH) receive antihypertensive agents. • In patients with LVH, initiation of treatment with one of the agents that have shown a greater ability to regress LVH should be considered, i.e. ACE inhibitors, angiotensin receptor blockers, and calcium antagonists. <u>Therapeutic strategies in hypertensive patients with atherosclerosis, arteriosclerosis, and peripheral artery disease (PAD)</u> • In the presence of carotid atherosclerosis, prescription of calcium antagonists and ACE inhibitors should be considered as these agents have shown a greater efficacy in delaying atherosclerosis progression than diuretics and β-blockers. • In hypertensive patients with a pulse wave velocity above 10 m/s, all antihypertensive drugs should be considered provided that a BP reduction to <140/90 mmHg is consistently achieved. • Antihypertensive therapy is recommended in hypertensive patients with PAD to achieve a goal of <140/90 mmHg, because of their high risk of myocardial infarction, stroke, heart failure, and CV death. • Though a careful follow up is necessary, β-blockers may be considered for the treatment of arterial hypertension in patients with PAD, since their use does not appear to be associated with exacerbation of PAD symptoms.
National Institute for Health and Clinical Excellence:	<u>Choosing antihypertensive drug treatment</u> • Where possible, recommend treatment with drugs taken only once a day. • Prescribe non-proprietary drugs where these are appropriate and minimize cost.

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Hypertension in adults: diagnosis and management (2011)[16]
 	
Reaffirmed Nov 2016
	• 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 people ≥80 years of age the same antihypertensive drug treatment as people aged 55 to 80 years, taking into account any comorbidities.
	• Offer antihypertensive drug treatment to women of child-bearing potential in line with the recommendations on Management of pregnancy with chronic hypertension and Breastfeeding in 'Hypertension in pregnancy' (NICE clinical guideline 107).
	
	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). 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 step one antihypertensive (ACE inhibitor, ARB) with a calcium channel blocker (CCB) to patients >55 years of age and to black patients of African or Caribbean family origin 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 chlorthalidone (12.5 to 25.0 mg once daily) or indapamide (1.5 mg modified-release once daily or 2.5 mg once daily) in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide.
	• For patients who are already receiving treatment with bendroflumethiazide or hydrochlorothiazide and whose blood pressure is stable and well controlled, continue treatment as is.
	• β-blockers are not a preferred initial therapy for hypertension; however, β-blockers may be considered in younger patients, particularly:
	  ○ Patients with an intolerance or contraindication to ACE inhibitors and ARBs.
	  ○ Women of child-bearing potential.
	  ○ People with evidence of increased sympathetic drive.
	• If treatment is initiated with a β-blocker and a second antihypertensive is required, add a CCB over a thiazide-like diuretic to reduce the risk of developing diabetes.
	
	Step two treatment
	• If blood pressure is not controlled with a step one antihypertensive, offer a step two treatment with a CCB in combination with an ACE inhibitor or an ARB.
	• If a CCB is not appropriate or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic.
	• For black patients of African or Caribbean family origin, consider an ARB in preference to an ACE inhibitor, in combination with a CCB.
	
	Step three treatment
	• Before considering step three treatment, review medication to ensure step two treatment is at optimal or best tolerated doses.
	• If three drugs are required to control blood pressure, the combination of an ACE inhibitor or ARB, CCB, and thiazide-like diuretic should be utilized.
	
	Step four treatment
	• Regard clinic blood pressure that remains >140/90 mmHg after treatment with the optimal or best tolerated doses of an ACE inhibitor or an ARB plus a CCB

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	plus a diuretic as resistant hypertension, and consider adding a fourth antihypertensive drug and/or seeking expert advice.
	• For treatment of resistant hypertension at step four:
	  ○ Consider further diuretic therapy with low-dose spironolactone (25 mg once daily) if the blood potassium level is 4.5 mmol/l or lower. Use particular caution in people with a reduced estimated glomerular filtration rate because they have an increased risk of hyperkalemia.
	  ○ Consider higher-dose thiazide-like diuretic treatment if the blood potassium level is higher than 4.5 mmol/l.
	  ○ If further diuretic therapy for resistant hypertension is not tolerated or is contraindicated or ineffective, consider an α-blocker or β-blocker.

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. • 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 (2012)**[18]	<u>Blood pressure management in chronic kidney disease (CKD) non-dialysis (ND) patients without diabetes mellitus</u> • The Work Group recommends that non-diabetic adults with CKD ND and urine albumin excretion <30 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >140 mm Hg systolic or >90 mm Hg diastolic be treated with blood pressure -lowering drugs to maintain a blood pressure that is consistently ≤140 mm Hg systolic and ≤90 mm Hg diastolic. • The Work Group suggests that non-diabetic adults with CKD ND and urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with BP-lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic. • The Work Group suggests that non-diabetic adults with CKD ND and urine albumin excretion >300 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with blood pressure -lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤ 80 mm Hg diastolic. • The Work Group suggests that an angiotensin receptor blocker (ARB) or angiotensin converting enzyme inhibitor (ACE-I) be used in non-diabetic adults with CKD ND and urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*) in whom treatment with blood pressure -lowering drugs is indicated.

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	• The Work Group recommends that an ARB or ACE-I be used in non-diabetic adults with CKD ND and urine albumin excretion >300 mg per 24 hours (or equivalent*) in whom treatment with blood pressure -lowering drugs is indicated. <u>Blood pressure management in CKD ND patients with diabetes mellitus</u> • The Work Group recommends that adults with diabetes and CKD ND with urine albumin excretion <30 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >140 mm Hg systolic or >90 mm Hg diastolic be treated with BP-lowering drugs to maintain a blood pressure that is consistently ≤140 mm Hg systolic and ≤90 mm Hg diastolic. • The Work Group suggests that adults with diabetes and CKD ND with urine albumin excretion >30 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with BP-lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic. • The Work Group suggests that an ARB or ACE-I be used in adults with diabetes and CKD ND with urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*). • The Work Group recommends that an ARB or ACE-I be used in adults with diabetes and CKD ND with urine albumin excretion >300 mg per 24 hours (or equivalent*). <u>Blood pressure management in kidney transplant recipients (non–dialysis-dependent CKD of any stage with a kidney transplant [CKD T])</u> • The Work Group suggests that adult kidney transplant recipients whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic, irrespective of the level of urine albumin excretion. • In adult kidney transplant recipients, choose a blood pressure -lowering agent after taking into account the time after transplantation, use of calcineurin inhibitors, presence or absence of persistent albuminuria, and other co morbid conditions. <u>Blood pressure management in children with CKD ND</u> • The Work Group recommends that in children with CKD ND, blood pressure -lowering treatment is started when blood pressure is consistently above the 90th percentile for age, sex, and height. • The Work Group suggests that in children with CKD ND (particularly those with proteinuria), blood pressure is lowered to consistently achieve systolic and diastolic readings less than or equal to the 50th percentile for age, sex, and height, unless achieving these targets is limited by signs or symptoms of hypotension. • The Work Group suggests that an ARB or ACE-I be used in children with CKD ND in whom treatment with blood pressure -lowering drugs is indicated, irrespective of the level of proteinuria. <u>Blood pressure management in elderly persons with CKD ND</u> • Tailor blood pressure treatment regimens in elderly patients with CKD ND by carefully considering age, co-morbidities and other therapies, with gradual escalation of treatment and close attention to adverse events related to blood pressure treatment, including electrolyte disorders, acute deterioration in kidney function, orthostatic hypotension and drug side effects. *Approximate equivalents for albumin excretion rate per 24 hours is expressed as protein excretion rate per 24 hours, albumin/creatinine ratio, protein/creatinine ratio, and protein reagent strip results.

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American Diabetes Association: **Standards of Medical Care in Diabetes (2017)**[19]	Hypertension/blood pressure control • Blood pressure should be measured at every routine visit. Patients found to have elevated blood pressure should have blood pressure confirmed on a separate day. • Most patients with diabetes and hypertension should be treated to a systolic blood pressure goal of <140 mmHg and a diastolic blood pressure goal of <90 mmHg. • Lower systolic and diastolic blood pressure targets, such as 130/80 mmHg, may be appropriate for individuals at high risk of cardiovascular disease, if they can be achieved without undue treatment burden. • In pregnant patients with diabetes and chronic hypertension, blood pressure targets of 120 to 160/80 to 105 mmHg are suggested in the interest of optimizing long-term maternal health and minimizing impaired fetal growth. • Patients with confirmed office-based blood pressure >140/90 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). 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. • For patients with blood pressure >120/80 mmHg, lifestyle intervention consists of weight loss if overweight or obese; a Dietary Approaches to Stop Hypertension–style dietary pattern including reducing sodium and increasing potassium intake; moderation of alcohol intake; and increased physical activity. Coronary heart disease • In asymptomatic patients, routine screening for coronary artery disease is not recommended as it does not improve outcomes as long as atherosclerotic cardiovascular disease risk factors are treated. • Consider investigations for coronary artery disease in the presence of any of the following: atypical cardiac symptoms (e.g., unexplained dyspnea, chest discomfort); signs or symptoms of associated vascular disease including carotid bruits, transient ischemic attack, stroke, claudication, or peripheral arterial disease; or electrocardiogram abnormalities (e.g., Q waves). • In patients with known atherosclerotic cardiovascular disease, use aspirin and statin therapy (if not contraindicated) and consider ACE inhibitor therapy to reduce the risk of cardiovascular events. • In patients with prior myocardial infarction, β-blockers should be continued for at least two years after the event. • In patients with symptomatic heart failure, thiazolidinedione treatment should not be used. • In patients with type 2 diabetes with stable congestive heart failure, metformin may be used if estimated glomerular filtration remains >30 mL/min but should be

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	avoided in unstable or hospitalized patients with congestive heart failure. Diabetic 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, in all patients with type 2 diabetes, and in all patients with comorbid hypertension. • Optimize glucose control to reduce the risk or slow the progression of diabetic kidney disease. • Optimize blood pressure control to reduce the risk or slow the progression of diabetic kidney disease. • For people with nondialysis-dependent diabetic kidney disease, dietary protein intake should be approximately 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. • 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) B 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 or changes in potassium when ACE inhibitors, angiotensin receptor blockers, or diuretics are used. • Continued monitoring of urinary albumin–to–creatinine ratio in patients with albuminuria treated with an ACE inhibitor or an angiotensin receptor blocker is reasonable to assess the response to treatment and progression of diabetic kidney disease. • An ACE inhibitor or an angiotensin receptor blocker is not recommended for the primary prevention of diabetic kidney disease 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. • When estimated glomerular filtration rate is <60 mL/min/1.73 m^2, evaluate and manage potential complications of chronic kidney disease. • Patients should be referred for evaluation for renal replacement treatment if they have an estimated glomerular filtration rate <30 mL/min/1.73 m^2. • Promptly refer to a physician experienced in the care of kidney disease for uncertainty about the etiology of kidney disease, difficult management issues, and rapidly progressing kidney disease.
National Heart, Lung, and Blood Institute: **Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (2012)**[20]	• Losartan, amlodipine, felodipine, fosinopril, lisinopril, metoprolol, and valsartan can be added to the list of medications that are tolerated over short periods, and can reduce blood pressure in children from ages 6 to 17 years, but predominantly is effective in adolescents. For African American children, greater doses of fosinopril may be needed for effective blood pressure control. Trial durations, however, were short, and long-term safety is still in question. For children from birth to age three years: • Routine measurement of blood pressure is not recommended. Blood pressure should be measured when there is a suspicion of renal disease, coarctation of the aorta, or other condition that may be associated with blood pressure elevation. • In these young patients, auscultation of blood pressure is often quite difficult, so measurement with an oscillometric device using an appropriate size cuff is acceptable. The state of the infant or young child (e.g., sleeping, quiet, fussing, crying) is important in the interpretation of blood pressure measurement. • For younger patients, treatment of high blood pressure is often directed at the underlying cause, since primary hypertension is uncommon.

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	For children, ages 3 to 11 years: • Routine measurement of blood pressure during health care visits is recommended. This is true of visits for health maintenance and for visits when the child is ill. • Auscultation should be the method of choice for confirmation of elevated blood pressure measurements using an oscillometric device. The blood pressure percentiles from the *Fourth Report* based on age, gender, and height percentiles should be used to categorize blood pressure as prehypertension or Stage 1 or Stage 2 hypertension. Blood pressure elevation must be persistent to be considered hypertension. • In this age group, obesity is an increasingly important cause of blood pressure elevation. When obesity is present, therapy should first be directed at improving diet and physical activity behaviors. This age group offers the opportunity to intervene early in the process of obesity development, allowing the clinician to focus on weight maintenance while the child grows, as opposed to weight loss. It also provides an important opportunity to introduce the Dietary Approaches to Stop Hypertension (DASH)-style diet. For adolescents, ages 12 to 17 years: • The approach to the evaluation of blood pressure is similar to that of children ages three to younger than 12 years, but the prevalence of primary hypertension is much more common, and obesity is a major concern as an underlying factor. • Adolescents with obesity are at risk of type 2 diabetes mellitus. Diabetes is a condition for which more aggressive blood pressure lowering is recommended. • In this age group, the level of blood pressure indicating prehypertension is at least 120/80, the same as that for adults. This is because the 90th percentile for adolescents is higher than 120/80 for most ages and height percentiles. • For adolescents with increased body mass index and elevated blood pressure, weight loss is the cornerstone of therapy. Both dietary and physical activity behaviors should be addressed, aiming for appropriate energy balance, lower dietary sodium, and a DASH-like dietary pattern. For young adults, ages 18 to 21 years: • Adult cut points for blood pressure in this age group are used to define hypertension. • In this age range, institution of the adult DASH diet is recommended for individuals with prehypertension or hypertension, as is reduction of dietary sodium. Overweight continues to be a major concern in this age group; weight reduction should be promoted through enhanced energy expenditure coupled with reduced energy intake. Physical activity should be promoted, since moderate-to-vigorous physical activity reduces blood pressure levels in adults. • The management of hypertension should follow the recommendations in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.

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[6,8-12]

Indication	Single Entity Agents			Combination Products
	Clonidine	Guanfacine	Methyldopa	Methyldopa and HCTZ
Treatment of hypertension	✔ *	✔ *	✔	✔ †

HCTZ=hydrochlorothiazide
*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[7]

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
Combination Products					
Methyldopa and HCTZ	Not reported	Not reported	Not reported	Not reported	Not reported

HCTZ=hydrochlorothiazide, 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[7]

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.
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.
Thiazide diuretics (HCTZ)	Dofetilide	Thiazide diuretics may induce hypokalemia which may increase the risk of torsades de pointes.
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.

Generic Name(s)	Interaction	Mechanism
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.
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.

HCTZ=hydrochlorothiazide

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.[6,7] The boxed warning for methyldopa-hydrochlorothiazide is listed in Table 7.

Table 6. Adverse Drug Events (%) Reported with the Central Alpha-Agonists[6-12]

Adverse Events	Single Entity Agents				Combination Products
	Clonidine Oral	Clonidine Transdermal	Guanfacine	Methyldopa	Methyldopa and HCTZ
Cardiovascular					
Angina	-	-	-	✔	✔
Arrhythmia	✔	-	-	-	-
Atrioventricular block	✔	-	-	-	-
Bradycardia	✔	-	≤3	✔	✔
Carotid sinus sensitivity	-	-	-	✔	✔
Chest pain	<1	-	≤3	-	-
Congestive heart failure	✔	-	-	✔	✔
Edema	-	-	-	✔	✔
Electrocardiogram abnormalities	✔	-	-	-	-
Hypotension	-	-	-	✔	✔
Myocarditis	-	-	-	✔	✔
Necrotizing angitis	-	-	-	-	✔
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	✔	-	-	✔	✔

Adverse Events	Single Entity Agents				Combination Products
	Clonidine Oral	Clonidine Transdermal	Guanfacine	Methyldopa	Methyldopa and HCTZ
Depression	✔	-	≤3	1 to 10	✔
Dizziness	16	2	12 to 15	✔	✔
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	-	-
Vertigo	-	-	-	-	✔
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	-	-	✔

Adverse Events	Single Entity Agents				Combination Products
	Clonidine Oral	Clonidine Transdermal	Guanfacine	Methyldopa	Methyldopa and HCTZ
Photosensitivity	-	-	-	-	✔
Pruritus	7	15 to 50	≤3	-	-
Purpura	-	-	≤3	-	✔
Rash	✔	-	-	✔	✔
Stevens Johnson syndrome	-	-	-	-	✔
Sweating	-	-	≤3	<1	-
Throbbing	-	3	-	-	-
Toxic epidermal necrolysis	-	-	-	✔	✔
Urticaria	✔	<1	-	-	✔
Vasculitis	-	-	-	✔	✔
Vesiculation	-	7	-	-	✔
Endocrine and Metabolic					
Breast enlargement	-	-	-	✔	✔
Erectile dysfunction	✔	-	-	-	-
Electrolyte imbalance	-	-	-	-	✔
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	✔	✔
Cramping	-	-	-	-	✔
Diarrhea	-	-	≤3	✔	✔
Distention	-	-	-	✔	✔
Dry mouth	40	25	10 to 54	1 to 10	✔
Dry throat	-	2	-	-	-
Dyspepsia	-	-	≤3	-	-
Dysphagia	-	-	≤3	-	-
Flatus	-	-	-	✔	✔

Adverse Events	Single Entity Agents				Combination Products
	Clonidine Oral	Clonidine Transdermal	Guanfacine	Methyldopa	Methyldopa and HCTZ
Gastritis	-	-	-	-	✔
Nausea	5	1	≤3	✔	✔
Pseudo-obstruction	✔	-	-	-	-
Parotitis	✔	-	-	-	-
Salivary gland pain	✔	-	-	-	-
Sialadenitis	-	-	-	✔	✔
Sore tongue	-	-	-	✔	✔
Taste alteration	-	1	≤3	-	-
Vomiting	5	-	-	✔	✔
Weight gain	1	-	-	✔	✔
Genitourinary					
Glucosuria	-	-	-	-	✔
Interstitial nephritis	-	-	-	-	✔
Micturition difficulties	✔	-	-	-	-
Nocturia	✔	-	-	-	-
Renal dysfunction	-	-	-	-	✔
Renal failure	-	-	-	-	✔
Testicular disorder	-	-	≤3	-	-
Urinary incontinence	-	-	≤3	<1	-
Urinary retention	1	-	-	-	-
Hematologic					
Agranulocytosis	-	-	-	-	✔
Aplastic anemia	-	-	-	-	✔
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	✔	-	-	✔	✔

Adverse Events	Single Entity Agents				Combination Products
	Clonidine Oral	Clonidine Transdermal	Guanfacine	Methyldopa	Methyldopa and HCTZ
Jaundice	-	-	-	✔	✔
Laboratory Test Abnormalities					
Blood urea nitrogen increased	-	-	-	✔	✔
Electrolyte disturbance	-	-	-	-	✔
Creatinine phosphokinase increased	✔	-	-	-	-
Hyperglycemia	✔	-	-	-	✔
Hyperuricemia	-	-	-	-	✔
Liver function test abnormalities	✔	-	-	✔	✔
Musculoskeletal					
Arthralgia	-	-	-	✔	✔
Hypokinesia	-	-	≤3	-	-
Leg cramps	✔	-	≤3	-	-
Muscle spasms	-	-	-	-	✔
Myalgia	✔	-	-	✔	-
Respiratory					
Dyspnea	-	-	≤3	<1	✔
Respiratory distress	-	-	-	-	✔
Rhinitis	-	-	≤3	-	-
Other					
Anaphylaxis	-	-	-	-	✔
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	✔	-	-	-	-
Xanthopsia	-	-	-	-	✔

✔ Percent not specified
- Event not reported

Table 7. Boxed Warning for Methyldopa and Hydrochlorothiazide[6,12]

WARNING
This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

VII. Dosing and Administration

The usual dosing regimens for the central α-agonists are listed in Table 8.

Table 8. Usual Dosing Regimens for the Central Alpha-Agonists[6-12]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Clonidine	Hypertension: 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.	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
Combination Products			
Methyldopa and HCTZ	Hypertension: Tablet: initial, 250-15 mg two or three times a day or 250-25 mg twice daily; maximum, HCTZ 50 mg and methyldopa 3 g daily	Safety and efficacy in children have not been established.	Tablet: 250-15 mg 250-25 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Dosage must be individualized, as determined by titration of the individual components. Once the patient has been successfully titrated, methyldopa and HCTZ may be substituted if the previously determined titrated doses are the same as in the combination.		

HCTZ=hydrochlorothiazide

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the central α-agonists are summarized in Table 9.

Table 9. 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.[21] (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.[22] (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
Boyles et al.[23] (1984) Methyldopa 250 to	OL, RCT Patients ≥59 years with isolated	N=21 18 weeks	Primary: Changes in blood pressure from baseline	Primary: At two weeks standing blood pressure fell from a mean of 166/90 mmHg at baseline to 164/88 mmHg with HCTZ monotherapy.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
800 mg/day and HCTZ 25 to 100 mg/day vs HCTZ 25 to 100 mg/day	systolic HTN		Secondary: Not reported	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.[24] (1981) Methyldopa 250 mg/day and HCTZ 15 mg/day vs chlorthalidone 50 mg/day and reserpine 0.25 mg/day	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).
Finnerty et al.[25] (1979) Methyldopa 500 mg to 2,000 mg QD vs reserpine 0.125 mg to 0.25 mg QD vs propranolol 80 mg	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
to 320 mg QD All patients received hydro-flumethiazide* 50 or 100 mg QD.				
Fernandez et al.[26] (1980) Methyldopa 750 mg/day vs chlorothiazide 450 mg/day vs methyldopa and chlorothiazide 250-150 mg/day* (fixed-dose combination product) vs placebo	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).
Materson et al.[27] (1990) Hydralazine 25, 50 or 100 mg BID vs	DB, MC, RCT Men ≥60 years with HTN not currently receiving antihypertensive therapy and DBP 90 to 114 mm Hg and	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	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,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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.	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		heart rate Secondary: The rates of drug intolerances, adverse effects	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%).
McAreavey et al.[28] (1984) Hydralazine 12.5 mg QD up to 100 mg BID	DB, PG, RCT Patients with inadequately controlled HTN while receiving	N=238 6 months	Primary: Comparative safety and efficacy, target blood pressure <140/95 mm Hg	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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 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.	atenolol 100 mg/day and bendrofluazide* 5 mg/day		Secondary: 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

*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	tablet, transdermal patch	Catapres®*, Catapres-TTS®*	$$$	$
Guanfacine	tablet	N/A	$$$$$	$
Methyldopa	tablet	N/A	N/A	$
Combination Products				
Methyldopa and HCTZ	tablet	N/A	N/A	$$$

*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.[6-12] 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.[1,13-20] 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.[1,13-20] Methyldopa is safe and effective to use during pregnancy.[14-15]

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.[22,23] There does not appear to be any difference in efficacy with the oral or transdermal formulations of clonidine.[21] According to treatment guidelines, most patients will need more than one antihypertensive agent to achieve blood pressure goals.[1,13-20] Certain guidelines note that that fixed combination antihypertensive medications can favor compliance and simplify medication regimens.[14] 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.[6-12]

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
November 8, 2017

I. Overview

The direct vasodilators are approved for the treatment of heart failure and hypertension, as well as for the treatment of hypoglycemia due to hyperinsulinism.[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. Hydralazine and minoxidil are available in a generic formulation. This class was last reviewed in August 2015.

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

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.
American Society of Hypertension/ International Society of Hypertension: **Clinical Practice Guidelines for the Management of Hypertension in the Community (2014)**[6]	Nonpharmacologic treatment • In patients with hypertension that is no more severe than stage one and is not associated with evidence of abnormal cardiovascular findings or other cardiovascular risks, six to 12 months of lifestyle changes can be attempted in the hope that they may be sufficiently effective to make it unnecessary to use medicines. • It may be prudent to start treatment with drugs sooner if it is clear that the blood pressure is not responding to the lifestyle methods or if other risk factors appear. • Weight loss: In patients who are overweight or obese, weight loss is helpful in treating hypertension, diabetes, and lipid disorders. • Salt reduction: Reduction of salt intake is recommended because it can reduce blood pressure and decrease the need for medications in patients who are "salt sensitive." • Exercise: Regular aerobic exercise can help reduce blood pressure. • Alcohol consumption: Up to two drinks a day can be helpful in protecting against cardiovascular events, but greater amounts of alcohol can raise blood pressure and should therefore be discouraged. In women, alcohol should be limited to one drink a day. • Cigarette smoking: Stopping smoking will not reduce blood pressure, but since smoking by itself is such a major cardiovascular risk factor, patients must be strongly urged to discontinue this habit. Drug treatment of hypertension • Treatment with drugs should be started in patients with blood pressures >140/90 mm Hg in whom lifestyle treatments have not been effective. • In patients with stage two hypertension (blood pressure ≥160/100 mm Hg), drug treatment should be started immediately after diagnosis, usually with a two-drug combination, without waiting to see the effects of lifestyle changes.

Clinical Guideline	Recommendations

	• For patients older than 80 years, the suggested threshold for starting treatment is at levels ≥150/90 mm Hg. Thus, the target of treatment should be <140/90 mm Hg for most patients but <150/90 mm Hg for older patients (unless these patients have chronic kidney disease or diabetes, when <140/90 mm Hg can be considered).
	• Most patients will require more than one drug to achieve control of their blood pressure.
	• In general, increase the dose of drugs or add new drugs at approximately two to three week intervals. This frequency can be faster or slower depending on the judgment of the practitioner. In general, the initial doses of drugs chosen should be at least half of the maximum dose so that only one dose adjustment is required thereafter. It is generally anticipated that most patients should reach an effective treatment regimen, whether one, two, or three drugs, within six to eight weeks.
	• Choice of drugs should be influenced by the age, ethnicity/race, and other clinical characteristics of the patient.
	• The choice of drugs will also be influenced by other conditions (e.g., diabetes and coronary disease) associated with the hypertension. Pregnancy also influences drug choice.
	• Long-acting drugs that need to be taken only once daily are preferred to shorter-acting drugs that require multiple doses because patients are more likely to follow a simple treatment regimen.
	• This guideline only makes recommendations for drug classes, not individual agents. There is an assumption, unless otherwise stated, that all drugs in a class are similar to each other.
	• Drug selectin when hypertension is the only or main concern:
	  ○ For black patients of all ages, use calcium channel blocker (CCB) or thiazide diuretic as first drug, then add angiotensin receptor blocker (ARB) or angiotensin-converting enzyme (ACE) inhibitor if needed.
	  ○ For white and other non-black patients <60 years of age, use ARB or ACE inhibitor as first drug, then add CCB or thiazide diuretic if needed.
	  ○ For white and other non-black patients ≥60 years of age, use CCB or thiazide diuretic as first drug, then add ARB or ACE inhibitor if needed.
	• Drug selection when hypertension is associated with other conditions:
	  ○ For patients with hypertension and diabetes, use ARB or ACE inhibitor as first drug (note, in black patients it is acceptable to start with a CCB or thiazide), then add CCB or thiazide diuretic (unless starting on CCB or thiazide in black patients) if needed.
	  ○ For patients with hypertension and chronic kidney disease, use ARB or ACE inhibitor as first drug, then add CCB or thiazide diuretic if needed.
	  ○ For patients with hypertension and clinical coronary artery disease, use β-blocker plus ARB or ACE inhibitor as first drugs, then add CCB or thiazide diuretic if needed.
	  ○ For patients with hypertension and stroke history, use ACE inhibitor or ARB as first drug, then add thiazide diuretic or CCB if needed.
	• For patients with hypertension and heart failure, patients with h symptomatic heart failure should usually receive an ARB or ACE inhibitor plus β-blocker plus diuretic plus spironolactone regardless of blood pressure. A dihydropyridine CCB can be added if needed for blood pressure control.

Hypertension Canada: **2017 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in**	<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.

Clinical Guideline	Recommendations

Adults (2017)[7]	• 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.
	
	<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>Guidelines for individuals 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. Treatment of hypertension in association with stroke • BP management in acute ischemic stroke (onset to 72 hours) ○ For patients with ischemic stroke not eligible for thrombolytic therapy, treatment of hypertension in the setting of acute ischemic stroke or transient ischemic attack should not be routinely undertaken. Extreme BP increases

Clinical Guideline	Recommendations
	(e.g., SBP >220 mmHg or DBP >120 mmHg) may be treated to reduce the BP by approximately 15%, and not more than 25%, over the first 24 hours with gradual reduction thereafter. Avoid excessive lowering of BP because this might exacerbate existing ischemia or might induce ischemia, particularly in the setting of intracranial arterial occlusion or extracranial carotid or vertebral artery occlusion. Pharmacological agents and routes of administration should be chosen to avoid precipitous decreases in BP. ○ For patients with ischemic stroke eligible for thrombolytic therapy, very high BP (>185/110 mmHg) should be treated concurrently in patients receiving thrombolytic therapy for acute ischemic stroke to reduce the risk of secondary intracranial hemorrhage. • 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) ○ For patients with intracerebral hemorrhage (ICH) in the hyperacute phase (in the first 24 hours) SBP lowering to <140 mmHg should be avoided because of an absence of benefit (relative to a target of <180 mmHg) and some suggestion of harm. <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> • For patients with nondiabetic chronic kidney disease, target BP is <140/90 mmHg. • For patients with hypertension and proteinuric chronic kidney disease (urinary protein >500 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. • Thiazide/thiazide-like diuretics are recommended as additive antihypertensive therapy. For patients with chronic kidney disease and volume overload, loop diuretics are an alternative. • 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,

Clinical Guideline	Recommendations
	progressive renal function loss, and acute pulmonary edema. • Patients with confirmed renal fibromuscular dysplasia (FMD) should be referred to a hypertension specialist. • In patients with hypertension attributable to FMD-related renal artery stenosis, revascularization should be considered. • 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. Combination therapy using two first-line agents may also be considered as initial treatment of hypertension if SBP is 20 mmHg greater than target or if DBP is 10 mmHg greater than target. However, caution should be exercised in patients in whom a substantial decrease in BP is more likely or poorly tolerated (e.g., elderly patients and patients with autonomic neuropathy). • 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.
European Society of Hypertension/European Society of Cardiology: **2013 Guidelines for the management of arterial hypertension (2013)**[8]	The 2013 guidelines on hypertension of the European Society of Hypertension and the European Society of Cardiology follow the guidelines jointly issued by the two societies in 2003 and 2007. <u>Treatment strategies and choice of antihypertensive drugs</u> • Diuretics (including thiazides, chlorthalidone, and indapamide), β-blockers, calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) are all suitable for the initiation and maintenance of antihypertensive treatment, either as monotherapy or in some combinations. • Some agents should be considered as the preferential choice in specific conditions because used in trials in those conditions or because of greater effectiveness in specific types of organ damage. • Initiation of antihypertensive therapy with a two-drug combination may be considered in patients with markedly high baseline blood pressure (BP) or at high cardiovascular (CV) risk. • The combination of two antagonists of the renin-angiotensin system (RAS) is not recommended and should be discouraged. • Other drug combinations should be considered and probably are beneficial in proportion to the extent of BP reduction. However, combinations that have been successfully used in trials may be preferable. • Combinations of two antihypertensive drugs at fixed doses in a single tablet may be recommended and favored, because reducing the number of daily pills improves adherence, which is low in patients with hypertension.

Clinical Guideline	Recommendations
	Treatment strategies in white-coat and masked hypertension • In white-coat hypertensives without additional risk factors, therapeutic intervention may be limited to lifestyle changes only, but this decision should be accompanied by close follow-up. • In white-coat hypertensives with a higher CV risk because of metabolic derangements or asymptomatic organ damage, drug treatment may be considered in addition to lifestyle changes. • In masked hypertension, both lifestyle measures and antihypertensive drug treatment should be considered, because this type of hypertension has been consistently found to have a CV risk very close to that of in- and out-of-office hypertension. Antihypertensive treatment strategies in the elderly • In elderly hypertensives with SBP ≥160 mmHg there is solid evidence to recommend reducing SBP to between 150 and 140 mmHg. • In fit elderly patients <80 years old antihypertensive treatment may be considered at SBP values ≥140 mmHg with a target SBP <140 mmHg if treatment is well tolerated. • In individuals older than 80 years with an initial SBP ≥160 mmHg, it is recommended to reduce SBP to between 150 and 140 mmHg, provided they are in good physical and mental conditions. • In frail elderly patients, it is recommended to leave decisions on antihypertensive therapy to the treating physician, and based on monitoring of the clinical effects of treatment. • Continuation of well-tolerated antihypertensive treatment should be considered when a treated individual becomes an octogenarian. • All hypertensive agents are recommended and can be used in the elderly, although diuretics and calcium antagonists may be preferred in isolated systolic hypertension. Treatment strategies in hypertensive women • Hormone therapy and selective estrogen receptor modulators are not recommended and should not be used for primary or secondary prevention of CVD. • If treatment of younger perimenopausal women is considered for severe menopausal symptoms, the benefits should be weighed against potential risks. • Drug treatment of severe hypertension in pregnancy (SBP >160 mmHg or DBP >110 mmHg) is recommended. • Drug treatment may also be considered in pregnant women with persistent elevation of BP ≥150/95 mmHg, and in those with BP ≥140/90 mmHg in the presence of gestational hypertension, subclinical organ damage or symptoms. • In women at high risk of pre-eclampsia, provided they are at low risk of gastrointestinal hemorrhage, treatment with low dose aspirin from 12 weeks until delivery may be considered. • In women with child-bearing potential RAS blockers are not recommended and should be avoided. • Methyldopa, labetalol, and nifedipine should be considered preferential antihypertensive drugs in pregnancy. Intravenous labetalol or infusion of nitroprusside should be considered in case of emergency (pre-eclampsia). Treatment strategies in patients with diabetes • While initiation of antihypertensive drug treatment in diabetic patients whose SBP is ≥160 mmHg is mandatory, it is strongly recommended to start drug treatment also when SBP is ≥140 mmHg. • A SBP goal <140 mmHg is recommended in patients with diabetes.

Clinical Guideline	Recommendations
	• The DBP target in patients with diabetes is recommended to be <85 mmHg. • All classes of antihypertensive agents are recommended and can be used in patients with diabetes; RAS blockers may be preferred, especially in the presence of proteinuria or microalbuminuria. • It is recommended that individual drug choice takes comorbidities into account. • Simultaneous administration of two blockers of the RAS is not recommended and should be avoided in patients with diabetes <u>Treatment strategies in hypertensive patients with metabolic syndrome</u> • Lifestyle changes, particularly weight loss and physical exercise, are to be recommended to all individuals with the metabolic syndrome. These interventions improve not only BP, but the metabolic components of the syndrome and delay diabetes onset. • As the metabolic syndrome can be considered a 'pre-diabetic' state, antihypertensive agents potentially improving or at least not worsening insulin sensitivity, such as RAS blockers and calcium antagonists, should be considered as the preferred drugs. Beta-blockers (with the exception of vasodilating β-blockers) and diuretics should be considered only as additional drugs, preferably in association with a potassium-sparing agent. • It is recommended to prescribe antihypertensive drugs with particular care in hypertensive patients with metabolic disturbances when BP is ≥140/90 mmHg after a suitable period of lifestyle changes, and to maintain BP <140/90 mmHg. • BP lowering drugs are not recommended in individuals with metabolic syndrome and high normal BP. <u>Therapeutic strategies in hypertensive patients with nephropathy</u> • Lowering SBP to <140 mmHg should be considered. • When overt proteinuria is present, SBP values <130 mmHg may be considered, provided that changes in eGFR are monitored. • RAS blockers are more effective in reducing albuminuria than other antihypertensive agents, and are indicated in hypertensive patients in the presence of microalbuminuria or overt proteinuria. • Reaching BP goals usually requires combination therapy, and it is recommended to combine RAS blockers with other antihypertensive agents. • Combination of two RAS blockers, though potentially more effective in reducing proteinuria, is not recommended. • Aldosterone antagonists cannot be recommended in chronic kidney disease (CKD), especially in combination with a RAS blocker, because of the risk of excessive reduction in renal function and of hyperkalemia. <u>Therapeutic strategies in hypertensive patients with cerebrovascular disease</u> • It is not recommended to intervene with BP-lowering therapy during the first week after acute stroke irrespective of BP level, although clinical judgement should be used in the face of very high SBP values. • Antihypertensive treatment is recommended in hypertensive patients with a history of stroke or transient ischemic attack (TIA), even when initial SBP is in the 140 to 159 mmHg range. • In hypertensive patients with a history of stroke or TIA, a SBP goal of <140 mmHg should be considered. • In elderly hypertensives with previous stroke or TIA, SBP values for intervention and goal may be considered to be somewhat higher. • All drug regimens are recommended for stroke prevention, provided that BP is effectively reduced. <u>Therapeutic strategies in hypertensive patients with heart disease</u>

Clinical Guideline	Recommendations
	• In hypertensive patients with CHD, a SBP goal <140 mmHg should be considered. • In hypertensive patients with a recent myocardial infarction, β-blockers are recommended. In case of other CHD all antihypertensive agents can be used, but β-blockers and calcium antagonists are to be preferred for symptomatic reasons (angina). • Diuretics, β-blockers, ACE inhibitors, angiotensin receptor blockers, and/or mineralocorticoid receptor antagonists are recommended in patients with heart failure or severe left ventricular (LV) dysfunction to reduce mortality and hospitalization. • In patients with heart failure and preserved ejection fraction (EF), there is no evidence that antihypertensive therapy per se or any particular drug is beneficial. However, in these patients, as well as in patients with hypertension and systolic dysfunction, lowering SBP to around 140 mmHg should be considered. Treatment guided by relief of symptoms (congestion with diuretics, high heart rate with β-blockers, etc.) should also be considered. • ACE inhibitors and angiotensin receptor blockers (and β-blockers and mineralocorticoid receptor antagonists if heart failure coexists) should be considered as antihypertensive agents in patients at risk of new or recurrent atrial fibrillation. • It is recommended that all patients with left ventricular hypertrophy (LVH) receive antihypertensive agents. • In patients with LVH, initiation of treatment with one of the agents that have shown a greater ability to regress LVH should be considered, i.e. ACE inhibitors, angiotensin receptor blockers, and calcium antagonists. Therapeutic strategies in hypertensive patients with atherosclerosis, arteriosclerosis, and peripheral artery disease (PAD) • In the presence of carotid atherosclerosis, prescription of calcium antagonists and ACE inhibitors should be considered as these agents have shown a greater efficacy in delaying atherosclerosis progression than diuretics and β-blockers. • In hypertensive patients with a pulse wave velocity above 10 m/s, all antihypertensive drugs should be considered provided that a BP reduction to <140/90 mmHg is consistently achieved. • Antihypertensive therapy is recommended in hypertensive patients with PAD to achieve a goal of <140/90 mmHg, because of their high risk of myocardial infarction, stroke, heart failure, and CV death. • Though a careful follow up is necessary, β-blockers may be considered for the treatment of arterial hypertension in patients with PAD, since their use does not appear to be associated with exacerbation of PAD symptoms.
National Institute for Health and Clinical Excellence: **Hypertension in adults: diagnosis and management (2011)**[9] **Reaffirmed Nov 2016**	Choosing antihypertensive drug treatment • 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 people ≥80 years of age the same antihypertensive drug treatment as people aged 55 to 80 years, taking into account any comorbidities. • Offer antihypertensive drug treatment to women of child-bearing potential in line with the recommendations on Management of pregnancy with chronic hypertension and Breastfeeding in 'Hypertension in pregnancy' (NICE clinical guideline 107). Step one treatment • Patients <55 years of age should be offered a step one antihypertensive with an

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	angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). 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 step one antihypertensive (ACE inhibitor, ARB) with a calcium channel blocker (CCB) to patients >55 years of age and to black patients of African or Caribbean family origin 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 chlorthalidone (12.5 to 25.0 mg once daily) or indapamide (1.5 mg modified-release once daily or 2.5 mg once daily) in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide.
	• For patients who are already receiving treatment with bendroflumethiazide or hydrochlorothiazide and whose blood pressure is stable and well controlled, continue treatment as is.
	• β-blockers are not a preferred initial therapy for hypertension; however, β-blockers may be considered in younger patients, particularly:
	  ○ Patients with an intolerance or contraindication to ACE inhibitors and ARBs.
	  ○ Women of child-bearing potential.
	  ○ People with evidence of increased sympathetic drive.
	• If treatment is initiated with a β-blocker and a second antihypertensive is required, add a CCB over a thiazide-like diuretic to reduce the risk of developing diabetes.
	
	<u>Step two treatment</u>
	• If blood pressure is not controlled with a step one antihypertensive, offer a step two treatment with a CCB in combination with an ACE inhibitor or an ARB.
	• If a CCB is not appropriate or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic.
	• For black patients of African or Caribbean family origin, consider an ARB in preference to an ACE inhibitor, in combination with a CCB.
	
	<u>Step three treatment</u>
	• Before considering step three treatment, review medication to ensure step two treatment is at optimal or best tolerated doses.
	• If three drugs are required to control blood pressure, the combination of an ACE inhibitor or ARB, CCB, and thiazide-like diuretic should be utilized.
	
	<u>Step four treatment</u>
	• Regard clinic blood pressure that remains >140/90 mmHg after treatment with the optimal or best tolerated doses of an ACE inhibitor or an ARB plus a CCB plus a diuretic as resistant hypertension, and consider adding a fourth antihypertensive drug and/or seeking expert advice.
	• For treatment of resistant hypertension at step four:
	  ○ Consider further diuretic therapy with low-dose spironolactone (25 mg once daily) if the blood potassium level is 4.5 mmol/l or lower. Use particular caution in people with a reduced estimated glomerular filtration rate because they have an increased risk of hyperkalemia.
	  ○ Consider higher-dose thiazide-like diuretic treatment if the blood potassium level is higher than 4.5 mmol/l.
	  ○ If further diuretic therapy for resistant hypertension is not tolerated or is contraindicated or ineffective, consider an α-blocker or β-blocker.

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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 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 (2012)[11]**	<u>Blood pressure management in chronic kidney disease (CKD) non-dialysis (ND) patients without diabetes mellitus</u> • The Work Group recommends that non-diabetic adults with CKD ND and urine albumin excretion <30 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >140 mm Hg systolic or >90 mm Hg diastolic be treated with blood pressure -lowering drugs to maintain a blood pressure that is consistently ≤140 mm Hg systolic and ≤90 mm Hg diastolic. • The Work Group suggests that non-diabetic adults with CKD ND and urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with BP-lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic. • The Work Group suggests that non-diabetic adults with CKD ND and urine albumin excretion >300 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with blood pressure -lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤ 80 mm Hg diastolic. • The Work Group suggests that an angiotensin receptor blocker (ARB) or angiotensin converting enzyme inhibitor (ACE-I) be used in non-diabetic adults with CKD ND and urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*) in whom treatment with blood pressure -lowering drugs is indicated. • The Work Group recommends that an ARB or ACE-I be used in non-diabetic adults with CKD ND and urine albumin excretion >300 mg per 24 hours (or equivalent*) in whom treatment with blood pressure -lowering drugs is indicated. <u>Blood pressure management in CKD ND patients with diabetes mellitus</u> • The Work Group recommends that adults with diabetes and CKD ND with urine albumin excretion <30 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >140 mm Hg systolic or >90 mm Hg diastolic be

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	treated with BP-lowering drugs to maintain a blood pressure that is consistently ≤140 mm Hg systolic and ≤90 mm Hg diastolic. • The Work Group suggests that adults with diabetes and CKD ND with urine albumin excretion >30 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with BP-lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic. • The Work Group suggests that an ARB or ACE-I be used in adults with diabetes and CKD ND with urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*). • The Work Group recommends that an ARB or ACE-I be used in adults with diabetes and CKD ND with urine albumin excretion >300 mg per 24 hours (or equivalent*). <u>Blood pressure management in kidney transplant recipients (non–dialysis-dependent CKD of any stage with a kidney transplant [CKD T])</u> • The Work Group suggests that adult kidney transplant recipients whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic, irrespective of the level of urine albumin excretion. • In adult kidney transplant recipients, choose a blood pressure -lowering agent after taking into account the time after transplantation, use of calcineurin inhibitors, presence or absence of persistent albuminuria, and other co morbid conditions. <u>Blood pressure management in children with CKD ND</u> • The Work Group recommends that in children with CKD ND, blood pressure -lowering treatment is started when blood pressure is consistently above the 90th percentile for age, sex, and height. • The Work Group suggests that in children with CKD ND (particularly those with proteinuria), blood pressure is lowered to consistently achieve systolic and diastolic readings less than or equal to the 50th percentile for age, sex, and height, unless achieving these targets is limited by signs or symptoms of hypotension. • The Work Group suggests that an ARB or ACE-I be used in children with CKD ND in whom treatment with blood pressure -lowering drugs is indicated, irrespective of the level of proteinuria. <u>Blood pressure management in elderly persons with CKD ND</u> • Tailor blood pressure treatment regimens in elderly patients with CKD ND by carefully considering age, co-morbidities and other therapies, with gradual escalation of treatment and close attention to adverse events related to blood pressure treatment, including electrolyte disorders, acute deterioration in kidney function, orthostatic hypotension and drug side effects. *Approximate equivalents for albumin excretion rate per 24 hours is expressed as protein excretion rate per 24 hours, albumin/creatinine ratio, protein/creatinine ratio, and protein reagent strip results.
American Diabetes Association: **Standards of Medical Care in Diabetes (2017)**[12]	<u>Hypertension/blood pressure control</u> • Blood pressure should be measured at every routine visit. Patients found to have elevated blood pressure should have blood pressure confirmed on a separate day. • Most patients with diabetes and hypertension should be treated to a systolic blood pressure goal of <140 mmHg and a diastolic blood pressure goal of <90 mmHg.

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	• Lower systolic and diastolic blood pressure targets, such as 130/80 mmHg, may be appropriate for individuals at high risk of cardiovascular disease, if they can be achieved without undue treatment burden. • In pregnant patients with diabetes and chronic hypertension, blood pressure targets of 120 to 160/80 to 105 mmHg are suggested in the interest of optimizing long-term maternal health and minimizing impaired fetal growth. • Patients with confirmed office-based blood pressure >140/90 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). 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. • For patients with blood pressure >120/80 mmHg, lifestyle intervention consists of weight loss if overweight or obese; a Dietary Approaches to Stop Hypertension–style dietary pattern including reducing sodium and increasing potassium intake; moderation of alcohol intake; and increased physical activity. <u>Coronary heart disease</u> • In asymptomatic patients, routine screening for coronary artery disease is not recommended as it does not improve outcomes as long as atherosclerotic cardiovascular disease risk factors are treated. • Consider investigations for coronary artery disease in the presence of any of the following: atypical cardiac symptoms (e.g., unexplained dyspnea, chest discomfort); signs or symptoms of associated vascular disease including carotid bruits, transient ischemic attack, stroke, claudication, or peripheral arterial disease; or electrocardiogram abnormalities (e.g., Q waves). • In patients with known atherosclerotic cardiovascular disease, use aspirin and statin therapy (if not contraindicated) and consider ACE inhibitor therapy to reduce the risk of cardiovascular events. • In patients with prior myocardial infarction, β-blockers should be continued for at least two years after the event. • In patients with symptomatic heart failure, thiazolidinedione treatment should not be used. • In patients with type 2 diabetes with stable congestive heart failure, metformin may be used if estimated glomerular filtration remains >30 mL/min but should be avoided in unstable or hospitalized patients with congestive heart failure. <u>Diabetic 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

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	diabetes with duration of five or more years, in all patients with type 2 diabetes, and in all patients with comorbid hypertension. • Optimize glucose control to reduce the risk or slow the progression of diabetic kidney disease. • Optimize blood pressure control to reduce the risk or slow the progression of diabetic kidney disease. • For people with nondialysis-dependent diabetic kidney disease, dietary protein intake should be approximately 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. • 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) B 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 or changes in potassium when ACE inhibitors, angiotensin receptor blockers, or diuretics are used. • Continued monitoring of urinary albumin–to–creatinine ratio in patients with albuminuria treated with an ACE inhibitor or an angiotensin receptor blocker is reasonable to assess the response to treatment and progression of diabetic kidney disease. • An ACE inhibitor or an angiotensin receptor blocker is not recommended for the primary prevention of diabetic kidney disease 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. • When estimated glomerular filtration rate is <60 mL/min/1.73 m^2, evaluate and manage potential complications of chronic kidney disease. • Patients should be referred for evaluation for renal replacement treatment if they have an estimated glomerular filtration rate <30 mL/min/1.73 m^2. • Promptly refer to a physician experienced in the care of kidney disease for uncertainty about the etiology of kidney disease, difficult management issues, and rapidly progressing kidney disease.
American College of Cardiology Foundation/ American Heart Association: **ACCF/AHA Guideline for the Management of Heart Failure (2013)**[13]	<u>ACCF/AHA Stages of Heart Failure (HF)</u> • Stage A: At high risk for HF but without structural heart disease or symptoms of HF. • Stage B: Structural heart disease but without signs or symptoms of HF. • Stage C: Structural heart disease with prior or current symptoms of HF. • Stage D: Refractory HF requiring specialized interventions. <u>Treatment of Stage A: Recommendations</u> • Hypertension and lipid disorders should be controlled in accordance with contemporary guidelines to lower the risk of HF. • Other conditions that may lead to or contribute to HF, such as obesity, diabetes mellitus, tobacco use, and known cardiotoxic agents, should be controlled or avoided. <u>Treatment of Stage B: Recommendations</u> • In all patients with a recent or remote history of myocardial infarction (MI) or acute coronary syndrome (ACS) and reduced ejection fraction (EF), ACE inhibitors should be used to prevent symptomatic HF and reduce mortality. In patients intolerant of ACE inhibitors, ARBs are appropriate unless contraindicated. • In all patients with a recent or remote history of MI or ACS and reduced EF,

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	evidence-based β-blockers should be used to reduce mortality. • In all patients with a recent or remote history of MI or ACS, statins should be used to prevent symptomatic HF and cardiovascular events. • In patients with structural cardiac abnormalities, including left ventricular (LV) hypertrophy, in the absence of a history of MI or ACS, blood pressure should be controlled in accordance with clinical practice guidelines for hypertension to prevent symptomatic HF. • ACE inhibitors should be used in all patients with a reduced EF to prevent symptomatic HF, even if they do not have a history of MI. • Beta-blockers should be used in all patients with a reduced EF to prevent symptomatic HF, even if they do not have a history of MI. • Nondihydropyridine calcium channel blockers with negative inotropic effects may be harmful in asymptomatic patients with low LVEF and no symptoms of HF after MI. <u>Treatment of Stage C HF with reduced EF (HFrEF): Recommendations</u> • Diuretics are recommended in patients with HFrEF who have evidence of fluid retention, unless contraindicated, to improve symptoms. • ACE inhibitors are recommended in patients with HFrEF and current or prior symptoms, unless contraindicated, to reduce morbidity and mortality. • ARBs are recommended in patients with HFrEF with current or prior symptoms who are ACE inhibitor intolerant, unless contraindicated, to reduce morbidity and mortality. • Use of one of the three β-blockers proven to reduce mortality (bisoprolol, carvedilol, and sustained-release metoprolol succinate) is recommended for all patients with current or prior symptoms of HFrEF, unless contraindicated, to reduce morbidity and mortality. • Aldosterone receptor antagonists (or mineralocorticoid receptor antagonists) are recommended in patients with NYHA class II to IV HF and who have LVEF of ≤35%, unless contraindicated, to reduce morbidity and mortality. Patients with NYHA class II HF should have a history of prior cardiovascular hospitalization or elevated plasma natriuretic peptide levels to be considered for aldosterone receptor antagonists. Creatinine should be ≤2.5 mg/dL in men or ≤2.0 mg/dL in women (or estimated glomerular filtration rate >30 mL/min/1.73 m2), and potassium should be less than 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. • The combination of hydralazine and isosorbide dinitrate is recommended to reduce morbidity and mortality for patients self-described as African Americans with NYHA class III to IV HFrEF receiving optimal therapy with ACE inhibitors and β-blockers, unless contraindicated. • Digoxin can be beneficial in patients with HFrEF, unless contraindicated, to decrease hospitalizations for HF. <u>Treatment of Stage C HF with preserved EF (HFpEF): Recommendations</u> • Systolic and diastolic blood pressure should be controlled in patients with HFpEF in accordance with published clinical practice guidelines to prevent morbidity. • Diuretics should be used for relief of symptoms due to volume overload in patients with HFpEF. • Management of AF according to published clinical practice guidelines in patients with HFpEF is reasonable to improve symptomatic HF. • The use of β-blocking agents, ACE inhibitors, and ARBs in patients with hypertension is reasonable to control blood pressure in patients with HFpEF.

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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)[14]**	<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
	  ○ 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;

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	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 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. ▪ Fibrinolytic therapy in patients with definite NSTE-ACS <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)

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	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. ○ 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

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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. ○ 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 patients treated with ticagrelor and 81 to 325 mg daily in all other patients. ○ 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. ○ 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 ○ 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. ○ 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.
Institute for Clinical Systems Improvement: **Heart Failure in Adults (2013)**[15]	Pharmacologic management: • Carvedilol, metoprolol succinate (extended-release) and bisoprolol have demonstrated reductions in mortality for patients with all classes of heart failure. These agents should be used before using other generic β-blockers. • ACE inhibitors should be prescribed for all patients with left ventricular systolic dysfunction unless contraindications are present. • If non-African American, ACE inhibitors are recommended for decreasing heart failure mortality than isosorbide dinitrate/hydralazine. In contrast, combination hydralazine and nitrates is recommended for patients self-described as African Americans, with moderate to severe symptoms on optimal therapy with ACE inhibitors, β-blockers, and diuretics. • ARBs should be considered primarily for patients who are intolerant to ACE inhibitors or in patients receiving standard drug therapy (including ACE inhibitors) who continue to show clinical deterioration. • Routine use of ARBs and ACE inhibitors and aldosterone antagonists cannot be recommended. • Diuretics should not be the sole therapy for patients with signs of volume overload; vasoactive drugs should be considered. • In severe heart failure, loop diuretics should be used over thiazide diuretics and combination therapy with thiazide. Loop diuretics are also effective in refractory cases of volume overload. • Patients with NYHA class III-IV heart failure on stable doses of digoxin and ACE inhibitors can reduce mortality by administering aldosterone-blocking agents. • Nesiritide is recommended to be reserved for patients with decompensated heart failure who remain volume overloaded despite aggressive treatment with diuretics/vasodilators display tolerance and/or resistance to vasodilators or diuretics, or demonstrate significant side effects to other vasodilators. • When considering the use of calcium channel blockers, only dihydropyridine

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	calcium channel blockers have been shown safe. Non-dihydropyridine calcium channel blockers can be used in patients with preserved systolic heart failure.
	
	<u>Pharmacologic management-digoxin</u>
	• In patients in normal sinus rhythm with preserved systolic function and mild to moderate heart failure symptoms on optimal therapy, digoxin had no effect on the endpoints of all-cause or cardiovascular mortality or hospitalization.
	• Serum levels less than 1.0 ng/mL are considered therapeutic. Levels greater than 1.2 have been associated with greater side effects. Serum levels do not always correlate to symptoms of digoxin toxicity.
	• Digoxin has been found useful:
	  o In heart failure patients with atrial fibrillation with a rapid ventricular response.
	  o In combination with ACE inhibitors in reducing hospitalizations in heart failure patients.
	• Digoxin should not:
	  o Be initiated in asymptomatic heart failure patients as it remains unsupported by clinical trials.
	  o Be "loaded" either orally or intravenously. Loading doses are generally not needed and steady state generally takes one week to reach.
	• Monitor for symptoms of toxicity, reduction of renal function or conduction abnormality.
	• To avoid digitalis toxicity, use lower doses in the elderly and those with renal impairment, check level in one to two weeks after start of therapy in elderly or renal-impaired patients, and be aware of drug interactions with new medications.
	• If continuing digoxin therapy in women, it may be reasonable to recommend that lower dosing (0.125 mg/day) should be used and lower serum levels (1.0 or less) should be maintained.

Heart Failure Society of America: **2010 Comprehensive Heart Failure Practice Guideline (2010)[16]**	<u>Patients with left ventricular systolic dysfunction</u> • ARBs are recommended in patients who cannot tolerate ACE inhibitors due to cough. The combination of hydralazine and an oral nitrate may be considered in such patients not tolerating ARB therapy. • Patients intolerant to ACE inhibitors from hyperkalemia or renal insufficiency are likely to experience the same side effects with ARBs. In these cases, the combination of hydralazine and an oral nitrate should be considered. • ARBs should be considered in patients experiencing angioedema while on ACE inhibitors based on their underlying risk and with recognition that angioedema has been reported infrequently with ARBs. The combination of hydralazine and oral nitrates may be considered in such patients not tolerating ARB therapy. • A combination of hydralazine and an oral nitrate is recommended in African American patients with heart failure and reduced left ventricular ejection fraction (LVEF) who are on a standard regimen of an ACE inhibitor (or ARB) and a β-blocker. • A combination of hydralazine and an oral nitrate may be considered in non–African American patients with heart failure and reduced LVEF who are symptomatic despite optimization of standard therapy. <u>Patients with hypertension and symptomatic left ventricular dysfunction with left ventricular dilation and low LVEF</u> • ACE inhibitors, ARBs, β-blockers, aldosterone inhibitors, and isosorbide dinitrate/hydralazine in various combinations (with a loop diuretic if needed) is recommended. <u>Managing heart failure in special populations</u>

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	• The combination of hydralazine/isosorbide dinitrate is recommended for African American women with moderate to severe heart failure symptoms who are on background neurohormonal inhibition. • A combination of hydralazine and isosorbide dinitrate is recommended as part of standard therapy in addition to β-blockers and ACE-inhibitors for African Americans with left ventricular systolic dysfunction and NYHA class II-IV heart failure.
European Society of Cardiology: **Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (2016)**[17]	Pharmacological treatments indicated in patients with symptomatic (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 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. • Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion. • 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. • 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. • 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). Recommendations for treatment of patients with heart failure with preserved ejection fraction and heart failure with mid-range ejection fraction • It is recommended to screen patients with HFpEF or HFmrEF (mid-range) for both cardiovascular and noncardiovascular comorbidities, which, if present, should be treated provided safe and effective interventions exist to improve

Clinical Guideline	Recommendations
	symptoms, well-being and/or prognosis. • Diuretics are recommended in congested patients with HFpEF or HFmrEF in order to alleviate symptoms and signs. <u>Recommendations for initial management of a rapid ventricular rate in patients with heart failure and atrial fibrillation in the acute or chronic setting</u> • Urgent electrical cardioversion is recommended if AF is thought to be contributing to the patient's hemodynamic compromise in order to improve the patient clinical condition. • For patients in NYHA Class IV, in addition to treatment for acute HF, an intravenous bolus of amiodarone or, in digoxin-naïve patients, an intravenous bolus of digoxin should be considered to reduce the ventricular rate. • For patients in NYHA Class I–III, a β-blocker, usually given orally, is safe and therefore is recommended as first-line treatment to control ventricular rate, provided the patient is euvolemic. • For patients in NYHA Class I–III, digoxin should be considered when ventricular rate remains high despite β-blockers or when β-blockers are not tolerated or contraindicated. • Treatment with dronedarone to improve ventricular rate control is not recommended due to safety concerns. <u>Recommendations for cardiac imaging in patients with suspected or established heart failure</u> • Transthoracic Echocardiogram (TTE) is recommended for the assessment of myocardial structure and function in subjects with suspected HF in order to establish a diagnosis of HFrEF, HFmrEF, or HFpEF. • TTE is recommended for the assessment of LVEF in order to identify patients with HF who would be suitable for evidence-based pharmacological and device treatment recommended for HFrEF. <u>Recommendations aiming to prevent or delay the development of overt heart failure or prevent death before the onset of symptoms</u> • Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life. • ACE inhibitor is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction in order to prevent or delay the onset of HF and prolong life. • β-blocker is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction, in order to prevent or delay the onset of HF and prolong life. <u>Pharmacological treatments indicated in patients with symptomatic 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 β-blocker is recommended, in addition to an ACE inhibitor, for patients with stable, symptomatic HFrEF to reduce the risk of HF hospitalization and death. • A mineralocorticoid receptor antagonist 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. <u>Other pharmacological treatments recommended in selected patients with symptomatic heart failure with reduced ejection fraction</u> • Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion.

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	• 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. Treatments (or combinations of treatments) that may cause harm in patients with symptomatic (New York Heart Association Class II–IV) heart failure with reduced ejection fraction • Diltiazem or verapamil are not recommended in patients with HFrEF, as they increase the risk of HF worsening and HF hospitalization. • The addition of an ARB (or a renin inhibitor) to the combination of an ACE inhibitor and a mineralocorticoid receptor antagonist is not recommended in patients with HF, because of the increased risk of renal dysfunction and hyperkalemia. Not-recommended treatments of co-morbidities in patients with heart failure • Thiazolidinediones (glitazones) are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization. • NSAIDs or COX-2 inhibitors are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization. Recommendations for the 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. • In patients with new-onset AHF or those with chronic, decompensated HF not receiving oral diuretics the initial recommended dose should be 20 to 40 mg intravenous furosemide (or equivalent); for those on chronic diuretic therapy, initial intravenous dose should be at least equivalent to oral dose. • It is recommended to give diuretics either as intermittent boluses or a continuous infusion, and the dose and duration should be adjusted according to the patients' symptoms and clinical status. • Inotropic agents are not recommended unless the patient is symptomatically hypotensive or hypoperfused because of safety concern.

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			✔

Indication	Single Entity Agents		Combination Products
	Hydralazine	Minoxidil	Isosorbide Dinitrate and Hydralazine
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 in such patients 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	-	-	✔
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

Adverse Events	Single Entity Agents		Combination Products
	Hydralazine	Minoxidil	Isosorbide Dinitrate and Hydralazine
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	-	-	✔
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

Adverse Events	Single Entity Agents		Combination Products
	Hydralazine	Minoxidil	Isosorbide Dinitrate and Hydralazine
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			

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
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.[18] (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[19] (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.[20] (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.[21] (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.[22] (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.[23] (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.[24] (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.[25] (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.[26] (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.[27] (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.[28] (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.[29] (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.[30] (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.[31] (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®	$$$$$	N/A

*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.[27-31] 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.[24] However, when hydralazine and isosorbide dinitrate were directly compared to an ACE inhibitor, mortality was significantly lower in the ACE inhibitor group.[25] 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.[13-17] 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).[3,19-22] 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.[13,16] 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
November 8, 2017

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
November 8, 2017

I. Overview

Fenoldopam is indicated for the in-hospital, short-term (up to 48 hours) management of severe hypertension in adults when rapid, but quickly reversible, emergency reduction of blood pressure is clinically indicated, including malignant hypertension with deteriorating end-organ function. In pediatric patients, fenoldopam is indicated for the in-hospital, short-term (up to four hours) reduction in blood pressure.[1]

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®.[2,3] 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.[2,4,5]

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 August 2015.

Table 1. Miscellaneous Hypotensive Agents Included in this Review

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

*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

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 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 Miscellaneous Hypotensive Agents[4]

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 4.

Table 3. Pharmacokinetic Parameters of the Miscellaneous Hypotensive Agents[5]

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.[4,6] 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.[4]

VI. Adverse Drug Events

The most common adverse reactions reported with the miscellaneous hypotensive agents are noted in Table 5.

Table 5. Adverse Events (%) Reported with the Miscellaneous Hypotensive Agents[4]

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 6.

Table 6. Usual Dosing for the Miscellaneous Hypotensive Agents[4]

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.[2]

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.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Alpha-Adrenergic Blocking Agents
AHFS Class 242000
November 8, 2017

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 August 2015.

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.

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.
American Society of Hypertension/ International Society of Hypertension: **Clinical Practice Guidelines for the Management of Hypertension in the Community (2014)**[18]	Nonpharmacologic treatment • In patients with hypertension that is no more severe than stage one and is not associated with evidence of abnormal cardiovascular findings or other cardiovascular risks, six to 12 months of lifestyle changes can be attempted in the hope that they may be sufficiently effective to make it unnecessary to use medicines. • It may be prudent to start treatment with drugs sooner if it is clear that the blood pressure is not responding to the lifestyle methods or if other risk factors appear. • Weight loss: In patients who are overweight or obese, weight loss is helpful in treating hypertension, diabetes, and lipid disorders. • Salt reduction: Reduction of salt intake is recommended because it can reduce blood pressure and decrease the need for medications in patients who are "salt sensitive." • Exercise: Regular aerobic exercise can help reduce blood pressure. • Alcohol consumption: Up to two drinks a day can be helpful in protecting against cardiovascular events, but greater amounts of alcohol can raise blood pressure and should therefore be discouraged. In women, alcohol should be limited to one drink a day. • Cigarette smoking: Stopping smoking will not reduce blood pressure, but since smoking by itself is such a major cardiovascular risk factor, patients must be strongly urged to discontinue this habit. Drug treatment of hypertension • Treatment with drugs should be started in patients with blood pressures >140/90 mm Hg in whom lifestyle treatments have not been effective. • In patients with stage two hypertension (blood pressure ≥160/100 mm Hg), drug treatment should be started immediately after diagnosis, usually with a two-drug

Clinical Guideline	Recommendations

	combination, without waiting to see the effects of lifestyle changes.
	• For patients older than 80 years, the suggested threshold for starting treatment is at levels ≥150/90 mm Hg. Thus, the target of treatment should be <140/90 mm Hg for most patients but <150/90 mm Hg for older patients (unless these patients have chronic kidney disease or diabetes, when <140/90 mm Hg can be considered).
	• Most patients will require more than one drug to achieve control of their blood pressure.
	• In general, increase the dose of drugs or add new drugs at approximately two to three week intervals. This frequency can be faster or slower depending on the judgment of the practitioner. In general, the initial doses of drugs chosen should be at least half of the maximum dose so that only one dose adjustment is required thereafter. It is generally anticipated that most patients should reach an effective treatment regimen, whether one, two, or three drugs, within six to eight weeks.
	• Choice of drugs should be influenced by the age, ethnicity/race, and other clinical characteristics of the patient.
	• The choice of drugs will also be influenced by other conditions (e.g., diabetes and coronary disease) associated with the hypertension. Pregnancy also influences drug choice.
	• Long-acting drugs that need to be taken only once daily are preferred to shorter-acting drugs that require multiple doses because patients are more likely to follow a simple treatment regimen.
	• This guideline only makes recommendations for drug classes, not individual agents. There is an assumption, unless otherwise stated, that all drugs in a class are similar to each other.
	• Drug selectin when hypertension is the only or main concern:
	  ○ For black patients of all ages, use calcium channel blocker (CCB) or thiazide diuretic as first drug, then add angiotensin receptor blocker (ARB) or angiotensin-converting enzyme (ACE) inhibitor if needed.
	  ○ For white and other non-black patients <60 years of age, use ARB or ACE inhibitor as first drug, then add CCB or thiazide diuretic if needed.
	  ○ For white and other non-black patients ≥60 years of age, use CCB or thiazide diuretic as first drug, then add ARB or ACE inhibitor if needed.
	• Drug selection when hypertension is associated with other conditions:
	  ○ For patients with hypertension and diabetes, use ARB or ACE inhibitor as first drug (note, in black patients it is acceptable to start with a CCB or thiazide), then add CCB or thiazide diuretic (unless starting on CCB or thiazide in black patients) if needed.
	  ○ For patients with hypertension and chronic kidney disease, use ARB or ACE inhibitor as first drug, then add CCB or thiazide diuretic if needed.
	  ○ For patients with hypertension and clinical coronary artery disease, use β-blocker plus ARB or ACE inhibitor as first drugs, then add CCB or thiazide diuretic if needed.
	  ○ For patients with hypertension and stroke history, use ACE inhibitor or ARB as first drug, then add thiazide diuretic or CCB if needed.
	• For patients with hypertension and heart failure, patients with h symptomatic heart failure should usually receive an ARB or ACE inhibitor plus β-blocker plus diuretic plus spironolactone regardless of blood pressure. A dihydropyridine CCB can be added if needed for blood pressure control.

Hypertension Canada: **2017 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of**	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

Clinical Guideline	Recommendations

Hypertension in Adults (2017)[19]	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.
	
	<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>Guidelines for individuals 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

Clinical Guideline	Recommendations
	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. Treatment of hypertension in association with stroke • BP management in acute ischemic stroke (onset to 72 hours) ○ For patients with ischemic stroke not eligible for thrombolytic therapy, treatment of hypertension in the setting of acute ischemic stroke or transient

Clinical Guideline	Recommendations
	ischemic attack should not be routinely undertaken. Extreme BP increases (e.g., SBP >220 mmHg or DBP >120 mmHg) may be treated to reduce the BP by approximately 15%, and not more than 25%, over the first 24 hours with gradual reduction thereafter. Avoid excessive lowering of BP because this might exacerbate existing ischemia or might induce ischemia, particularly in the setting of intracranial arterial occlusion or extracranial carotid or vertebral artery occlusion. Pharmacological agents and routes of administration should be chosen to avoid precipitous decreases in BP. ○ For patients with ischemic stroke eligible for thrombolytic therapy, very high BP (>185/110 mmHg) should be treated concurrently in patients receiving thrombolytic therapy for acute ischemic stroke to reduce the risk of secondary intracranial hemorrhage. • 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) ○ For patients with intracerebral hemorrhage (ICH) in the hyperacute phase (in the first 24 hours) SBP lowering to <140 mmHg should be avoided because of an absence of benefit (relative to a target of <180 mmHg) and some suggestion of harm. <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> • For patients with nondiabetic chronic kidney disease, target BP is <140/90 mmHg. • For patients with hypertension and proteinuric chronic kidney disease (urinary protein >500 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. • Thiazide/thiazide-like diuretics are recommended as additive antihypertensive therapy. For patients with chronic kidney disease and volume overload, loop diuretics are an alternative. • 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

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	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. • In patients with hypertension attributable to FMD-related renal artery stenosis, revascularization should be considered. • 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. Combination therapy using two first-line agents may also be considered as initial treatment of hypertension if SBP is 20 mmHg greater than target or if DBP is 10 mmHg greater than target. However, caution should be exercised in patients in whom a substantial decrease in BP is more likely or poorly tolerated (e.g., elderly patients and patients with autonomic neuropathy). • 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.
European Society of Hypertension/European Society of Cardiology: **2013 Guidelines for the management of arterial hypertension (2013)**[20]	The 2013 guidelines on hypertension of the European Society of Hypertension and the European Society of Cardiology follow the guidelines jointly issued by the two societies in 2003 and 2007. Treatment strategies and choice of antihypertensive drugs • Diuretics (including thiazides, chlorthalidone, and indapamide), β-blockers, calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) are all suitable for the initiation and maintenance of antihypertensive treatment, either as monotherapy or in some combinations. • Some agents should be considered as the preferential choice in specific conditions because used in trials in those conditions or because of greater effectiveness in specific types of organ damage. • Initiation of antihypertensive therapy with a two-drug combination may be considered in patients with markedly high baseline blood pressure (BP) or at high cardiovascular (CV) risk. • The combination of two antagonists of the renin-angiotensin system (RAS) is not recommended and should be discouraged. • Other drug combinations should be considered and probably are beneficial in proportion to the extent of BP reduction. However, combinations that have been successfully used in trials may be preferable. • Combinations of two antihypertensive drugs at fixed doses in a single tablet may be recommended and favored, because reducing the number of daily pills improves adherence, which is low in patients with hypertension.

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	<u>Treatment strategies in white-coat and masked hypertension</u> • In white-coat hypertensives without additional risk factors, therapeutic intervention may be limited to lifestyle changes only, but this decision should be accompanied by close follow-up. • In white-coat hypertensives with a higher CV risk because of metabolic derangements or asymptomatic organ damage, drug treatment may be considered in addition to lifestyle changes. • In masked hypertension, both lifestyle measures and antihypertensive drug treatment should be considered, because this type of hypertension has been consistently found to have a CV risk very close to that of in- and out-of-office hypertension. <u>Antihypertensive treatment strategies in the elderly</u> • In elderly hypertensives with SBP ≥160 mmHg there is solid evidence to recommend reducing SBP to between 150 and 140 mmHg. • In fit elderly patients <80 years old antihypertensive treatment may be considered at SBP values ≥140 mmHg with a target SBP <140 mmHg if treatment is well tolerated. • In individuals older than 80 years with an initial SBP ≥160 mmHg, it is recommended to reduce SBP to between 150 and 140 mmHg, provided they are in good physical and mental conditions. • In frail elderly patients, it is recommended to leave decisions on antihypertensive therapy to the treating physician, and based on monitoring of the clinical effects of treatment. • Continuation of well-tolerated antihypertensive treatment should be considered when a treated individual becomes an octogenarian. • All hypertensive agents are recommended and can be used in the elderly, although diuretics and calcium antagonists may be preferred in isolated systolic hypertension. <u>Treatment strategies in hypertensive women</u> • Hormone therapy and selective estrogen receptor modulators are not recommended and should not be used for primary or secondary prevention of CVD. • If treatment of younger perimenopausal women is considered for severe menopausal symptoms, the benefits should be weighed against potential risks. • Drug treatment of severe hypertension in pregnancy (SBP >160 mmHg or DBP >110 mmHg) is recommended. • Drug treatment may also be considered in pregnant women with persistent elevation of BP ≥150/95 mmHg, and in those with BP ≥140/90 mmHg in the presence of gestational hypertension, subclinical organ damage or symptoms. • In women at high risk of pre-eclampsia, provided they are at low risk of gastrointestinal hemorrhage, treatment with low dose aspirin from 12 weeks until delivery may be considered. • In women with child-bearing potential RAS blockers are not recommended and should be avoided. • Methyldopa, labetalol, and nifedipine should be considered preferential antihypertensive drugs in pregnancy. Intravenous labetalol or infusion of nitroprusside should be considered in case of emergency (pre-eclampsia). <u>Treatment strategies in patients with diabetes</u> • While initiation of antihypertensive drug treatment in diabetic patients whose SBP is ≥160 mmHg is mandatory, it is strongly recommended to start drug treatment also when SBP is ≥140 mmHg.

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	• A SBP goal <140 mmHg is recommended in patients with diabetes. • The DBP target in patients with diabetes is recommended to be <85 mmHg. • All classes of antihypertensive agents are recommended and can be used in patients with diabetes; RAS blockers may be preferred, especially in the presence of proteinuria or microalbuminuria. • It is recommended that individual drug choice takes comorbidities into account. • Simultaneous administration of two blockers of the RAS is not recommended and should be avoided in patients with diabetes <u>Treatment strategies in hypertensive patients with metabolic syndrome</u> • Lifestyle changes, particularly weight loss and physical exercise, are to be recommended to all individuals with the metabolic syndrome. These interventions improve not only BP, but the metabolic components of the syndrome and delay diabetes onset. • As the metabolic syndrome can be considered a 'pre-diabetic' state, antihypertensive agents potentially improving or at least not worsening insulin sensitivity, such as RAS blockers and calcium antagonists, should be considered as the preferred drugs. Beta-blockers (with the exception of vasodilating β-blockers) and diuretics should be considered only as additional drugs, preferably in association with a potassium-sparing agent. • It is recommended to prescribe antihypertensive drugs with particular care in hypertensive patients with metabolic disturbances when BP is ≥140/90 mmHg after a suitable period of lifestyle changes, and to maintain BP <140/90 mmHg. • BP lowering drugs are not recommended in individuals with metabolic syndrome and high normal BP. <u>Therapeutic strategies in hypertensive patients with nephropathy</u> • Lowering SBP to <140 mmHg should be considered. • When overt proteinuria is present, SBP values <130 mmHg may be considered, provided that changes in eGFR are monitored. • RAS blockers are more effective in reducing albuminuria than other antihypertensive agents, and are indicated in hypertensive patients in the presence of microalbuminuria or overt proteinuria. • Reaching BP goals usually requires combination therapy, and it is recommended to combine RAS blockers with other antihypertensive agents. • Combination of two RAS blockers, though potentially more effective in reducing proteinuria, is not recommended. • Aldosterone antagonists cannot be recommended in chronic kidney disease (CKD), especially in combination with a RAS blocker, because of the risk of excessive reduction in renal function and of hyperkalemia. <u>Therapeutic strategies in hypertensive patients with cerebrovascular disease</u> • It is not recommended to intervene with BP-lowering therapy during the first week after acute stroke irrespective of BP level, although clinical judgement should be used in the face of very high SBP values. • Antihypertensive treatment is recommended in hypertensive patients with a history of stroke or transient ischemic attack (TIA), even when initial SBP is in the 140 to 159 mmHg range. • In hypertensive patients with a history of stroke or TIA, a SBP goal of <140 mmHg should be considered. • In elderly hypertensives with previous stroke or TIA, SBP values for intervention and goal may be considered to be somewhat higher. • All drug regimens are recommended for stroke prevention, provided that BP is effectively reduced.

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	Therapeutic strategies in hypertensive patients with heart disease • In hypertensive patients with CHD, a SBP goal <140 mmHg should be considered. • In hypertensive patients with a recent myocardial infarction, β-blockers are recommended. In case of other CHD all antihypertensive agents can be used, but β-blockers and calcium antagonists are to be preferred for symptomatic reasons (angina). • Diuretics, β-blockers, ACE inhibitors, angiotensin receptor blockers, and/or mineralocorticoid receptor antagonists are recommended in patients with heart failure or severe left ventricular (LV) dysfunction to reduce mortality and hospitalization. • In patients with heart failure and preserved ejection fraction (EF), there is no evidence that antihypertensive therapy per se or any particular drug is beneficial. However, in these patients, as well as in patients with hypertension and systolic dysfunction, lowering SBP to around 140 mmHg should be considered. Treatment guided by relief of symptoms (congestion with diuretics, high heart rate with β-blockers, etc.) should also be considered. • ACE inhibitors and angiotensin receptor blockers (and β-blockers and mineralocorticoid receptor antagonists if heart failure coexists) should be considered as antihypertensive agents in patients at risk of new or recurrent atrial fibrillation. • It is recommended that all patients with left ventricular hypertrophy (LVH) receive antihypertensive agents. • In patients with LVH, initiation of treatment with one of the agents that have shown a greater ability to regress LVH should be considered, i.e. ACE inhibitors, angiotensin receptor blockers, and calcium antagonists. Therapeutic strategies in hypertensive patients with atherosclerosis, arteriosclerosis, and peripheral artery disease (PAD) • In the presence of carotid atherosclerosis, prescription of calcium antagonists and ACE inhibitors should be considered as these agents have shown a greater efficacy in delaying atherosclerosis progression than diuretics and β-blockers. • In hypertensive patients with a pulse wave velocity above 10 m/s, all antihypertensive drugs should be considered provided that a BP reduction to <140/90 mmHg is consistently achieved. • Antihypertensive therapy is recommended in hypertensive patients with PAD to achieve a goal of <140/90 mmHg, because of their high risk of myocardial infarction, stroke, heart failure, and CV death. • Though a careful follow up is necessary, β-blockers may be considered for the treatment of arterial hypertension in patients with PAD, since their use does not appear to be associated with exacerbation of PAD symptoms.
National Institute for Health and Clinical Excellence: **Hypertension in adults: diagnosis and management (2011)**[21] **Reaffirmed Nov 2016**	Choosing antihypertensive drug treatment • 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 people ≥80 years of age the same antihypertensive drug treatment as people aged 55 to 80 years, taking into account any comorbidities. • Offer antihypertensive drug treatment to women of child-bearing potential in line with the recommendations on Management of pregnancy with chronic hypertension and Breastfeeding in 'Hypertension in pregnancy' (NICE clinical guideline 107). Step one treatment

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	• Patients <55 years of age should be offered a step one antihypertensive with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). 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 step one antihypertensive (ACE inhibitor, ARB) with a calcium channel blocker (CCB) to patients >55 years of age and to black patients of African or Caribbean family origin 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 chlorthalidone (12.5 to 25.0 mg once daily) or indapamide (1.5 mg modified-release once daily or 2.5 mg once daily) in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide.
	• For patients who are already receiving treatment with bendroflumethiazide or hydrochlorothiazide and whose blood pressure is stable and well controlled, continue treatment as is.
	• β-blockers are not a preferred initial therapy for hypertension; however, β-blockers may be considered in younger patients, particularly:
	  ○ Patients with an intolerance or contraindication to ACE inhibitors and ARBs.
	  ○ Women of child-bearing potential.
	  ○ People with evidence of increased sympathetic drive.
	• If treatment is initiated with a β-blocker and a second antihypertensive is required, add a CCB over a thiazide-like diuretic to reduce the risk of developing diabetes.
	
	<u>Step two treatment</u>
	• If blood pressure is not controlled with a step one antihypertensive, offer a step two treatment with a CCB in combination with an ACE inhibitor or an ARB.
	• If a CCB is not appropriate or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic.
	• For black patients of African or Caribbean family origin, consider an ARB in preference to an ACE inhibitor, in combination with a CCB.
	
	<u>Step three treatment</u>
	• Before considering step three treatment, review medication to ensure step two treatment is at optimal or best tolerated doses.
	• If three drugs are required to control blood pressure, the combination of an ACE inhibitor or ARB, CCB, and thiazide-like diuretic should be utilized.
	
	<u>Step four treatment</u>
	• Regard clinic blood pressure that remains >140/90 mmHg after treatment with the optimal or best tolerated doses of an ACE inhibitor or an ARB plus a CCB plus a diuretic as resistant hypertension, and consider adding a fourth antihypertensive drug and/or seeking expert advice.
	• For treatment of resistant hypertension at step four:
	  ○ Consider further diuretic therapy with low-dose spironolactone (25 mg once daily) if the blood potassium level is 4.5 mmol/l or lower. Use particular caution in people with a reduced estimated glomerular filtration rate because they have an increased risk of hyperkalemia.
	  ○ Consider higher-dose thiazide-like diuretic treatment if the blood potassium level is higher than 4.5 mmol/l.
	  ○ If further diuretic therapy for resistant hypertension is not tolerated or

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	is contraindicated or ineffective, consider an α-blocker or β-blocker.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in Blacks (2010)**[22]	• 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 (2012)**[23]	<u>Blood pressure management in chronic kidney disease (CKD) non-dialysis (ND) patients without diabetes mellitus</u> • The Work Group recommends that non-diabetic adults with CKD ND and urine albumin excretion <30 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >140 mm Hg systolic or >90 mm Hg diastolic be treated with blood pressure -lowering drugs to maintain a blood pressure that is consistently ≤140 mm Hg systolic and ≤90 mm Hg diastolic. • The Work Group suggests that non-diabetic adults with CKD ND and urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with BP-lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic. • The Work Group suggests that non-diabetic adults with CKD ND and urine albumin excretion >300 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with blood pressure -lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤ 80 mm Hg diastolic. • The Work Group suggests that an angiotensin receptor blocker (ARB) or angiotensin converting enzyme inhibitor (ACE-I) be used in non-diabetic adults with CKD ND and urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*) in whom treatment with blood pressure -lowering drugs is indicated. • The Work Group recommends that an ARB or ACE-I be used in non-diabetic adults with CKD ND and urine albumin excretion >300 mg per 24 hours (or equivalent*) in whom treatment with blood pressure -lowering drugs is indicated. <u>Blood pressure management in CKD ND patients with diabetes mellitus</u> • The Work Group recommends that adults with diabetes and CKD ND with urine albumin excretion <30 mg per 24 hours (or equivalent*) whose office

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	blood pressure is consistently >140 mm Hg systolic or >90 mm Hg diastolic be treated with BP-lowering drugs to maintain a blood pressure that is consistently ≤140 mm Hg systolic and ≤90 mm Hg diastolic. • The Work Group suggests that adults with diabetes and CKD ND with urine albumin excretion >30 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with BP-lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic. • The Work Group suggests that an ARB or ACE-I be used in adults with diabetes and CKD ND with urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*). • The Work Group recommends that an ARB or ACE-I be used in adults with diabetes and CKD ND with urine albumin excretion >300 mg per 24 hours (or equivalent*). <u>Blood pressure management in kidney transplant recipients (non–dialysis-dependent CKD of any stage with a kidney transplant [CKD T])</u> • The Work Group suggests that adult kidney transplant recipients whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic, irrespective of the level of urine albumin excretion. • In adult kidney transplant recipients, choose a blood pressure -lowering agent after taking into account the time after transplantation, use of calcineurin inhibitors, presence or absence of persistent albuminuria, and other co morbid conditions. <u>Blood pressure management in children with CKD ND</u> • The Work Group recommends that in children with CKD ND, blood pressure -lowering treatment is started when blood pressure is consistently above the 90th percentile for age, sex, and height. • The Work Group suggests that in children with CKD ND (particularly those with proteinuria), blood pressure is lowered to consistently achieve systolic and diastolic readings less than or equal to the 50th percentile for age, sex, and height, unless achieving these targets is limited by signs or symptoms of hypotension. • The Work Group suggests that an ARB or ACE-I be used in children with CKD ND in whom treatment with blood pressure -lowering drugs is indicated, irrespective of the level of proteinuria. <u>Blood pressure management in elderly persons with CKD ND</u> • Tailor blood pressure treatment regimens in elderly patients with CKD ND by carefully considering age, co-morbidities and other therapies, with gradual escalation of treatment and close attention to adverse events related to blood pressure treatment, including electrolyte disorders, acute deterioration in kidney function, orthostatic hypotension and drug side effects. *Approximate equivalents for albumin excretion rate per 24 hours is expressed as protein excretion rate per 24 hours, albumin/creatinine ratio, protein/creatinine ratio, and protein reagent strip results.
American Diabetes Association: **Standards of Medical Care in Diabetes (2017)**[24]	<u>Hypertension/blood pressure control</u> • Blood pressure should be measured at every routine visit. Patients found to have elevated blood pressure should have blood pressure confirmed on a separate day. • Most patients with diabetes and hypertension should be treated to a systolic blood pressure goal of <140 mmHg and a diastolic blood pressure goal of <90

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	mmHg. • Lower systolic and diastolic blood pressure targets, such as 130/80 mmHg, may be appropriate for individuals at high risk of cardiovascular disease, if they can be achieved without undue treatment burden. • In pregnant patients with diabetes and chronic hypertension, blood pressure targets of 120 to 160/80 to 105 mmHg are suggested in the interest of optimizing long-term maternal health and minimizing impaired fetal growth. • Patients with confirmed office-based blood pressure >140/90 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). 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. • For patients with blood pressure >120/80 mmHg, lifestyle intervention consists of weight loss if overweight or obese; a Dietary Approaches to Stop Hypertension–style dietary pattern including reducing sodium and increasing potassium intake; moderation of alcohol intake; and increased physical activity. <u>Coronary heart disease</u> • In asymptomatic patients, routine screening for coronary artery disease is not recommended as it does not improve outcomes as long as atherosclerotic cardiovascular disease risk factors are treated. • Consider investigations for coronary artery disease in the presence of any of the following: atypical cardiac symptoms (e.g., unexplained dyspnea, chest discomfort); signs or symptoms of associated vascular disease including carotid bruits, transient ischemic attack, stroke, claudication, or peripheral arterial disease; or electrocardiogram abnormalities (e.g., Q waves). • In patients with known atherosclerotic cardiovascular disease, use aspirin and statin therapy (if not contraindicated) and consider ACE inhibitor therapy to reduce the risk of cardiovascular events. • In patients with prior myocardial infarction, β-blockers should be continued for at least two years after the event. • In patients with symptomatic heart failure, thiazolidinedione treatment should not be used. • In patients with type 2 diabetes with stable congestive heart failure, metformin may be used if estimated glomerular filtration remains >30 mL/min but should be avoided in unstable or hospitalized patients with congestive heart failure. <u>Diabetic kidney disease</u> • At least once a year, assess urinary albumin (e.g., spot urinary albumin–to–

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	creatinine ratio) and estimated glomerular filtration rate in patients with type 1 diabetes with duration of five or more years, in all patients with type 2 diabetes, and in all patients with comorbid hypertension. • Optimize glucose control to reduce the risk or slow the progression of diabetic kidney disease. • Optimize blood pressure control to reduce the risk or slow the progression of diabetic kidney disease. • For people with nondialysis-dependent diabetic kidney disease, dietary protein intake should be approximately 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. • 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) B 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 or changes in potassium when ACE inhibitors, angiotensin receptor blockers, or diuretics are used. • Continued monitoring of urinary albumin–to–creatinine ratio in patients with albuminuria treated with an ACE inhibitor or an angiotensin receptor blocker is reasonable to assess the response to treatment and progression of diabetic kidney disease. • An ACE inhibitor or an angiotensin receptor blocker is not recommended for the primary prevention of diabetic kidney disease 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. • When estimated glomerular filtration rate is <60 mL/min/1.73 m^2, evaluate and manage potential complications of chronic kidney disease. • Patients should be referred for evaluation for renal replacement treatment if they have an estimated glomerular filtration rate <30 mL/min/1.73 m^2. • Promptly refer to a physician experienced in the care of kidney disease for uncertainty about the etiology of kidney disease, difficult management issues, and rapidly progressing kidney disease.
American Urological Association: **Update on American Urological Association Guideline on Management of Benign Prostatic Hyperplasia (2011)[8]** **(Reviewed 2014)**	<u>Watchful waiting</u> • Patients with mild symptoms of lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH) and patients with moderate or severe symptoms who are not bothered by their LUTS should be managed using a strategy of watchful waiting. <u>Medical management</u> • Alfuzosin, doxazosin, tamsulosin, and terazosin are appropriate and effective treatments for patients with bothersome, moderate to severe LUTS secondary to BPH. Although slight differences in adverse events profiles exist among these agents, all four appear to have equal clinical effectiveness. Although head-to-head trials comparing these agents are currently lacking, the available data support this contention. There were no published studies on silodosin in peer-reviewed literature prior to the cut-off date for the literature search for this guideline. • The older, less costly, generic α-adrenergic blocking agents remain reasonable choices. These agents require dose titration and blood pressure monitoring. • As prazosin and the nonselective α-adrenergic blocking agent phenoxybenzamine were not reviewed in the course of this guideline revision, the 2003 guideline statement indicating that the data were insufficient to support

Clinical Guideline	Recommendations
	a recommendation for the use of these two agents as treatments for LUTS secondary to BPH remains true. • The combination of an α-adrenergic blocking agent and a 5α-reductase inhibitor is an appropriate and effective treatment for patients with LUTS associated with demonstrable prostatic enlargement based on volume measurement, prostate specific antigen level as a proxy for volume and/or enlargement on digital rectal exam. • Men with LUTS secondary to BPH and with planned cataract surgery should avoid the initiation of α-adrenergic blocking agent until the completion of cataract surgery. • 5α-reductase inhibitors may be used to prevent progression of LUTS secondary to BPH and to reduce the risk of urinary retention and future prostate-related surgery. • 5α-reductase inhibitors should not be used in men with LUTS secondary to BPH without prostatic enlargement. • 5α-reductase inhibitors are an appropriate and effective treatment for men with LUTS secondary to BPH who have demonstrable prostate enlargement. • Finasteride is an appropriate and effective treatment in men with refractory hematuria presumably due to prostatic bleeding. Dutasteride may also be an effective agent based on expert opinion. • There is insufficient evidence to recommend using 5α-reductase inhibitors preoperatively for the prevention of bleeding during transurethral resection of the prostate. • Anticholinergic agents are an appropriate and effective treatment for the management of LUTS secondary to BPH in men without an elevated post-void residual volume and when LUTS are predominantly irritative. • Prior to initiation of an anticholinergic, baseline post-void residual urine should be assessed; use with caution in patients with a volume >250 to 300 mL. • No dietary supplement, combination phytotherapeutic agent or other nonconventional therapy is recommended for the management of LUTS secondary to BPH. • At this time, the available data do not suggest that saw palmetto has a clinically meaningful effect on LUTS secondary to BPH. • The paucity of published, high quality, single extract clinical trials of Urtica dioica do not provide a sufficient evidence base with which to recommend for or against its use for the treatment of LUTS secondary to BPH.
European Association of Urology: **Treatment of Non-Neurogenic Male Lower Urinary Tract Symptoms (LUTS) (2017)**[9]	Conservative treatment • Men with mild-to-moderate uncomplicated LUTS who are not too troubled by their symptoms are suitable for watchful waiting. Watchful waiting should consist of education, reassurance, periodic monitoring, and lifestyle advice. • Men with LUTS should always be offered lifestyle advice prior to or concurrent with treatment. Pharmacological management • α-adrenergic blocking agents should be offered to men with moderate to severe LUTS. • 5α-reductase inhibitors should be offered to men who have moderate to severe LUTS and an enlarged prostate. 5α-reductase inhibitors can prevent disease progression with regard to acute urinary retention and need for surgery. • Muscarinic receptor antagonists may be used in men with moderate to severe LUTS who have predominantly bladder storage symptoms; however, caution is advised in men with a post-void residual volume > 150 mL. • Phosphodiesterase 5 inhibitors reduce moderate to severe LUTS in men with or without erectile dysfunction.

Clinical Guideline	Recommendations
	• The Guidelines Panel has not made any specific recommendations on phytotherapy for the treatment of male LUTS because of product heterogeneity, limited regulatory framework, and methodological limitations of the published trials and meta-analyses. • Use β-3 agonists (mirabegron) in men with moderate-to-severe LUTS who mainly have bladder storage symptoms. Long-term studies on the efficacy and safety of mirabegron in men of any age with LUTS are not yet available. • Combination treatment with an α-adrenergic blocking agent and a 5α-reductase inhibitor can be offered to men with troublesome moderate-to-severe LUTS, enlarged prostate, and reduced Qmax (men likely to develop disease progression). Combination treatment with an α-adrenergic blocking agent and a muscarinic receptor antagonist may be considered in patients with troublesome moderate to severe LUTS if symptom relief has been insufficient with the monotherapy of either drug; however, caution is warranted in men with bladder outlet obstruction.

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 hypertension	✔		
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	-

Adverse Events	Doxazosin	Prazosin	Terazosin
Depersonalization	<1	-	-
Depression	1	1 to 4	-
Dizziness	5 to 19	10	9 to 19
Drowsiness	-	8	-
Emotional lability	<1	-	-
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

Adverse Events	Doxazosin	Prazosin	Terazosin
Renal calculus	<1	-	-
Sexual dysfunction	2	-	-
Urinary frequency	-	1 to 4	-
Urinary incontinence	1	<1	<1
Urinary tract infection	1	-	<1
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

Adverse Events	Doxazosin	Prazosin	Terazosin
Anaphylaxis	-	-	<1
Diaphoresis	1	✔	<1
Facial edema	1	-	<1
Infection	<1	-	-
Influenza-like symptoms	1	-	≤2
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.[25] (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.[26] (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.[27] (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.[28] (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.[29] (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.[30]	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.[31] (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.[32] (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.[33] (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.[34] (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.[35] (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.[36] (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.[37] (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.[38] (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.[39] (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.[40] (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.[41] (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.[42] (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.[43] (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.[44] (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.[45] (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.[46] (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.[47] (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.[48] (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.[49] (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.[50] (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.[51] (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.[52] (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.[53] (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.[54] (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.[55] (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.[56]	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.[57] (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.[58] (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.[59] (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.[60] (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.[61] (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.[62]	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.[63] (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.[64] (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.[65] (1987) Study 1: 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	Study 1: N=903 10 to 24 week trial; therapy continued for up to 62 weeks Study 2: 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 Study 2: Doxazosin 16 mg QD vs terazosin 20 mg QD				
Trost et al.[66] (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.[67] (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.[68] (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.[69] (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.[70] (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.[71] (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.[72] (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.[73]	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.[74] (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.[75] (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.[76] (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.[77] (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.[78] (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.[79] (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.[80] (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.[81] (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.[82] (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.[83] (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.[84]	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.[85] (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.[86] (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.[87] (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[88-90] (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.[91] (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.[92] (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.[93] (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.[25-54]

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.[17-24] 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.[17-19,20-22] Most patients will require more than one antihypertensive medication to achieve blood pressure goals.[17-24]

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.[55-87] 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.[88-91]

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.

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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.[1-22] Additionally, propranolol is the first agent Food and Drug Administration-approved for the treatment of proliferating infantile hemangioma requiring systemic therapy.[12,24] The β-blockers differ with regards to their adrenergic-receptor blocking, membrane stabilizing and intrinsic sympathomimetic activities, as well as lipophilicity.[1-23] 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.[23,25] 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.[23,25]

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.[1,2,17-22]

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 nebivolol and penbutolol. This class was last reviewed in August 2015.

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 tablet, injection, tablet	Lopressor®*, Toprol-XL®*	metoprolol
Nadolol	tablet	Corgard®*	nadolol
Nebivolol	tablet	Bystolic®	none
Penbutolol	tablet	Levatol®	none
Pindolol	tablet	N/A	pindolol
Propranolol	extended-release capsule, injection, solution, tablet	Hemangeol®, Inderal LA®*, Inderal XL®, InnoPran XL®	propranolol
Sotalol	injection, tablet, solution	Betapace®*, Betapace AF®*, Sorine®*, Sotylize®	sotalol

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
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	extended-release tablet, tablet	Dutoprol®	metoprolol and hydrochlorothiazide
Nadolol and bendroflumethiazide	tablet	Corzide®*	nadolol and bendroflumethiazide
Propranolol and hydrochlorothiazide	tablet	N/A	propranolol 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

Table 2. Selected Pharmacologic Properties of the Beta-Adrenergic Blocking Agents[1-22]

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
American College of Cardiology/American Heart Association: **2007 Chronic Angina Focused Update of the 2002 Guidelines for the Management of**	• Aspirin should be started at 75 to 162 mg/day and continued indefinitely in all patients, unless contraindicated. • Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with an increased risk of bleeding and should be monitored closely. • Patients with hypertension and established coronary artery disease (CAD) should be treated with blood pressure medication(s) as tolerated, including angiotensin converting enzyme (ACE) inhibitors and/or β-adrenergic antagonists (β-blockers) with the addition of other medications as needed to achieve blood pressure goals of

Clinical Guideline	Recommendations
Patients With Chronic Stable Angina (2007)[26]	<140/90 or <130/80 mm Hg for patients with chronic kidney disease or diabetes. • Long-acting calcium channel blocking agents or long-acting nitrates may be used if β-blockers are contraindicated. Immediate-release and short-acting dihydropyridine calcium channel blockers can increase adverse cardiac events and should not be used. • Long-acting calcium channel blockers or long-acting nitrates may be used with β-blockers if initial treatment is not successful. • ACE inhibitors should be used indefinitely in patients with a left ventricular ejection fraction (LVEF) ≤40% and in those with hypertension, diabetes or chronic kidney disease, unless contraindicated. • ACE inhibitors should also be used indefinitely in patients at lower risk (mildly reduced or normal LVEF in whom cardiovascular risk factors remain well controlled and revascularization has been performed), unless contraindicated. • Angiotensin II receptor blockers (ARBs) are recommended in patients with hypertension, those who have an indication for an ACE inhibitor and are intolerant to them, who have heart failure, or who have had a myocardial infarction (MI) and have a LVEF ≤40%. • ARBs may be considered in combination with an ACE inhibitor for heart failure due to left ventricular systolic dysfunction. • Aldosterone blockade is recommended in patients post-MI without significant renal dysfunction or hyperkalemia who are already receiving therapeutic doses of an ACE inhibitor and a β-blocker, have a LVEF ≤40% and have either diabetes or heart failure. • It is beneficial to start and continue β-blocker therapy indefinitely in all patients who have had a MI, acute coronary syndrome or left ventricular dysfunction with or without heart failure symptoms, unless contraindicated. • Annual influenza vaccination is recommended in patients with cardiovascular disease.
European Society of Cardiology: **Guidelines on the Management of Stable Coronary Artery Disease (2013)[27]**	<u>General management of stable coronary artery disease (SCAD) patients</u> • The goal of management of SCAD is to reduce symptoms and improve prognosis. • The management of CAD patients encompasses lifestyle modification, control of CAD risk factors, evidence-based pharmacological therapy, and patient education. <u>General considerations for pharmacological treatments in SCAD patients</u> • 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. <u>Pharmacological treatments for angina/ischemia relief in SCAD patients</u> • Short-acting nitrates are recommended. • First-line treatment is indicated with ß-blockers and/or calcium channel blockers to control heart rate and symptoms. • For second-line treatment it is recommended to add long-acting nitrates or ivabradine or nicorandil* or ranolazine, according to heart rate, blood pressure, and tolerance. • For second-line treatment, trimetazidine* may be considered. • 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 β-blockers avoided.

Clinical Guideline	Recommendations
	Pharmacological treatments for event prevention in SCAD patients • Low-dose aspirin daily is recommended in all SCAD patients. • Clopidogrel is indicated as an alternative in case of aspirin intolerance. • Statins are recommended in all SCAD patients. • It is recommended to use ACE inhibitors (or ARBs) if presence of other conditions (e.g. heart failure, hypertension or diabetes). Treatment in patients with microvascular angina • It is recommended that all patients receive secondary prevention medications including aspirin and statins. • β-blockers are recommended as a first line treatment. • Calcium antagonists are recommended if β-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 (aminophylline, bamiphylline*) or non-pharmacological treatments such as neurostimulatory techniques may be considered in patients with symptoms refractory to the above listed drugs.
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)**[28]	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**	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

Clinical Guideline	Recommendations
Cardiology Foundation Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes (2014)[29]	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; 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-

Clinical Guideline	Recommendations

	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 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

Clinical Guideline	Recommendations
	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 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.

Clinical Guideline	Recommendations

	• Late hospital and post-hospital oral antiplatelet therapy
	  ○ 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.
	  ○ 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.
	  ○ 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
	  ○ 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.
	  ○ 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: **Guideline for the Management of Acute Coronary Syndromes in Patients Presenting Without Persistent ST-Segment Elevation (2015)**[30]	Pharmacological treatment of ischemia
	• Early initiation of β-blocker treatment is recommended in patients with ongoing ischemic symptoms and without contraindications.
	• 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.
	
	Recommendations for platelet inhibition in non-ST-elevation acute coronary syndromes
	• 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.
	  ○ 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.
	• 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.

Clinical Guideline	Recommendations
	Recommendations for anticoagulation in non-ST-elevation acute coronary syndromes • 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. 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 CHADS2-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. • 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 CHADS2-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.

Clinical Guideline	Recommendations
	• In medically managed patients, one antiplatelet agent in addition to oral anticoagulant should be considered for up to one year.
American College of Cardiology/American Heart Association: **Guideline for the Management of ST-Elevation Myocardial Infarction (2013)**[31]	Routine medical therapies: β-blockers • 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. Routine medical therapies: Renin-Angiotensin-Aldosterone System Inhibitors • 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. 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 (2012)**[32]	Routine therapies in the acute, subacute and long term phase of STEMI • Active smokers with STEMI must receive counseling and be referred to a smoking cessation program. • Each hospital participating in the care of STEMI patients must have a smoking cessation protocol. • Exercise-based rehabilitation is recommended. • Antiplatelet therapy with low dose aspirin (75 to 100 mg) is indicated indefinitely after STEMI. • In patients intolerant to aspirin, clopidogrel is indicated as an alternative. • Dual antiplatelet therapy with a combination of aspirin and prasugrel or aspirin and ticagrelor is recommended (over aspirin and clopidogrel) in patients treated with PCI. • Dual antiplatelet therapy with aspirin and an oral ADP receptor antagonist must be continued for up to 12 months after STEMI, with a strict minimum of 1 month for patients receiving bare metal stent and 6 months for patients receiving drug-eluting stent. • In patients with left ventricular thrombus, anticoagulation should be instituted for a minimum of 3 months. • In patients with a clear indication for oral anticoagulation (e.g. atrial fibrillation with CHA2DS2-VASc Score ≥2 or mechanical valve prosthesis), oral anticoagulation must be implemented in addition to antiplatelet therapy. • If patients require triple antithrombotic therapy, combining dual antiplatelet therapy and oral anticoagulant, e.g. because of stent placement and an obligatory indication

Clinical Guideline	Recommendations
	for oral anticoagulation, the duration of dual antiplatelet therapy should be minimized to reduce bleeding risk. • 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 1 year in patients with STEMI who did not receive a stent. • Gastric protection with a proton pump inhibitor should be considered for the duration of DAPT therapy in patients at high risk of bleeding. • 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. • Intravenous β-blockers must be avoided in patients with hypotension or heart failure. • Intravenous β-blockers should be considered at the time of presentation in patients 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. • Reassessment of LDL-cholesterol should be considered after 4–6 weeks to ensure that a target value of ≤70 mg/dL has been reached. • Verapamil may be considered for secondary prevention in patients with absolute contraindications to β-blockers and no heart failure. • 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.

National Institute for Health and Clinical Excellence: **Myocardial Infarction: cardiac rehabilitation and prevention of further cardiovascular disease (2013)**[33]	Drug therapy
	• Offer all people who have had an acute MI treatment with the following drugs:
	  ○ ACE inhibitor
	  ○ Dual antiplatelet therapy (aspirin plus a second antiplatelet agent)
	  ○ β-blocker
	  ○ Statin
	
	Antiplatelet therapy
	• Offer aspirin to all people after an MI and continue indefinitely, unless they are aspirin intolerant or have an indication for anticoagulation.
	• Offer aspirin to people who have had an MI more than 12 months ago and continue it indefinitely.
	• For patients with aspirin hypersensitivity, clopidogrel monotherapy should be considered as an alternative treatment.
	• Special considerations should be made for people with dyspepsia.
	• After appropriate treatment, people with a history of aspirin-induced ulcer bleeding whose ulcers have healed and who are negative for *Helicobacter pylori* should be considered for treatment in line with dyspepsia.

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	• Ticagrelor in combination with low-dose aspirin is recommended for up to 12 months as a treatment option in adults with ACS (STEMI, PCI, or NSTEMI). • Offer clopidogrel as a treatment option for up to 12 months to people who have had an NSTEMI, regardless of treatment, or people who have had a STEMI and received a bare-metal or drug-eluting stent. • Offer clopidogrel as a treatment option for at least one month and consider continuing for up to 12 months in people who have had a STEMI and medical management with or without reperfusion treatment with a fibrinolytic agent. • Continue the second antiplatelet agent for up to 12 months in people who have had a STEMI and who received CABG surgery. • Offer clopidogrel instead of aspirin to people who also have other clinical vascular disease (had an MI and stopped dual antiplatelet therapy or had an MI more than 12 months ago). <u>Antiplatelet therapy in people with an indication for anticoagulation</u> • Take bleeding risk, thromboembolic risk, and cardiovascular risk into account when deciding which people who have had an MI and have an indication for anticoagulation. • Unless there is a high risk of bleeding, continue anticoagulation and add aspirin to treatment in people who have had an MI who otherwise need anticoagulation and who have had their condition managed medically or have undergone balloon angioplasty or have undergone CABG surgery. • Continue anticoagulation and add clopidogrel to treatment in people who have had an MI, who have undergone PCI with bare-metal or drug-eluting stents and who otherwise need anticoagulation. • Offer clopidogrel with warfarin to people with a sensitivity to aspirin who otherwise need anticoagulation and aspirin and who have had an MI. • Do not routinely offer warfarin in combination with prasugrel or ticagrelor to people who need anticoagulation who have had an MI. • After 12 months since the MI, continue anticoagulation and take into consideration the need for ongoing antiplatelet therapy, taking into account all of the following: indication for anticoagulation, thromboembolic risk, bleeding risk, cardiovascular risk and the person's wishes. • Do not add a new oral anticoagulant (rivaroxaban, apixaban or dabigatran) in combination with dual antiplatelet therapy in people who otherwise need anticoagulation, who have had an MI. • Consider using warfarin and discontinuing treatment with a new oral anticoagulant (rivaroxaban, apixaban, or dabigatran) in people who otherwise need anticoagulation and who have had an MI, unless there is a specific clinical indication to continue it.
American College of Cardiology/American Heart Association: **Guideline for the Management of Heart Failure (2013)**[34]	<u>Treatment of Stage A heart failure (HF)</u> • Hypertension and lipid disorders should be controlled in accordance with guidelines to lower the risk of HF. (Level of Evidence (LoE): A) • Other conditions that may lead to or contribute to HF, such as obesity, diabetes mellitus, tobacco use, and known cardiotoxic agents, should be controlled or avoided. (LoE: C) <u>Treatment of Stage B heart failure</u> • In patients with a history of MI and reduced EF, ACE inhibitors or ARBs should be used to prevent HF. (LoE: A) • In patients with MI and reduced EF, evidence-based β-blockers (using one of three proven to reduce mortality [i.e., bisoprolol, carvedilol, and sustained-release metoprolol succinate]) should be used to prevent HF. (LoE: B) • In patients with MI, statins should be used to prevent HF. (LoE: A) • ACE inhibitors and β-blockers should be used in all patients with a reduced EF to

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	prevent symptomatic HF, even if they do not have a history of MI. (LoE: A and C, respectively) • Blood pressure should be controlled to prevent symptomatic HF. (LoE: A) • Nondihydropyridine calcium channel blockers may be harmful in patients with low LVEF. (LoE: C) <u>Pharmacological treatment for Stage C HFrEF</u> • Recommendations for patients in Stages A and B are recommended where appropriate for patients in Stage C. (LoE: A, B, and C as appropriate) • Diuretics are recommended in patients with HFrEF who have evidence of fluid retention, unless contraindicated, to improve symptoms. (LoE: C) • ACE inhibitors are recommended in patients with HFrEF and current or prior symptoms, unless contraindicated, to reduce morbidity and mortality. ARBs are recommended as alternative therapy in ACE inhibitor intolerant patients. (LoE: A) • Use of one of the three β-blockers proven to reduce mortality is recommended for all patients with current or prior symptoms of HFrEF, unless contraindicated, to reduce morbidity and mortality. (LoE: A) • Aldosterone receptor antagonists are recommended in patients with NYHA class II–IV HF and who have LVEF of ≤35%, unless contraindicated, to reduce morbidity and mortality. Patients with NYHA class II HF should have a history of prior cardiovascular hospitalization or elevated plasma natriuretic peptide levels to be considered for aldosterone receptor antagonists. Creatinine should be ≤2.5 mg/dL in men or ≤2.0 mg/dL in women (or estimated glomerular filtration rate >30 mL/min/1.73 m^2), and potassium should be <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) • The combination of hydralazine and isosorbide dinitrate is recommended to reduce morbidity and mortality for patients self-described as African Americans with NYHA class III–IV HFrEF receiving optimal therapy with ACE inhibitors and β-blockers, unless contraindicated. (LoE: A) • Digoxin can be beneficial in patients with HFrEF, unless contraindicated, to decrease hospitalizations for HF. (LoE: B) • Patients with chronic HF with permanent/persistent/paroxysmal AF and an additional risk factor for cardioembolic stroke (history of hypertension, diabetes mellitus, previous stroke or transient ischemic attack, or ≥75 years of age) should receive chronic anticoagulant therapy. (LoE: A) • Statins are not beneficial as adjunctive therapy when prescribed solely for the diagnosis of HF in the absence of other indications for their use. (LoE: A) • Calcium channel blockers are not recommended as routine treatment for patients with HFrEF. (LoE: A) <u>Pharmacological treatment for Stage C HFpEF</u> • Blood pressure should be controlled according to published clinical practice guidelines. (LoE: B) • Diuretics should be used for relief of symptoms due to volume overload. (LoE: C) • The use of β-blocking agents, ACE inhibitors, and ARBs in patients with hypertension is reasonable to control blood pressure in patients with HFpEF. (LoE: C) <u>Treatment of Stage D (advanced/refractory) HF</u> • Fluid restriction (1.5 to 2 L/d) is reasonable, especially in patients with hyponatremia, to reduce congestive symptoms. (LoE: C) • Until definitive therapy (e.g., coronary revascularization, mechanical circulatory support, heart transplantation) or resolution of the acute precipitating problem,

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	patients with cardiogenic shock should receive temporary intravenous inotropic support to maintain systemic perfusion and preserve end-organ performance. (LoE: C) • Continuous intravenous inotropic support is reasonable as "bridge therapy" in patients with stage D HF refractory to medical therapy and device therapy who are eligible for and awaiting mechanical circulatory support or cardiac transplantation. (LoE: B) • Long-term use of either continuous or intermittent, intravenous parenteral positive inotropic agents, in the absence of specific indications or for reasons other than palliative care, is potentially harmful in the patient with HF. (LoE: B)
Heart Failure Society of America: **Heart Failure Society of America 2010 Comprehensive Heart Failure Practice Guidelines (Executive Summary) (2010)**[35]	Patients with left ventricular systolic dysfunction • ACE inhibitors should be used in all patients with a LVEF ≤40%, unless otherwise contraindicated. • ARBs may be used in patients who are intolerant to ACE inhibitors. Hydralazine and a nitrate may be used in patients intolerant to ACE inhibitors and ARBs, or in whom such therapy is contraindicated. • The combination of an ACE inhibitor and a β-blocker is recommended in all patients with a LVEF ≤40%. • The routine use of an ARB with a combination of an ACE inhibitor and β-blocker in patients who have had a MI and have left ventricular dysfunction is not recommended. • The addition of an ARB can be considered in patients with heart failure due to reduced LVEF who have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor and a β-blocker. • Individual ARBs may be considered as initial therapy (instead of an ACE inhibitor) in patients with heart failure who have had a MI and in patients with chronic heart failure and systolic dysfunction. • ARBs are recommended in patients who cannot tolerate ACE inhibitors due to cough. The combination of hydralazine and an oral nitrate may be considered in such patients not tolerating ARB therapy. • Patients intolerant to ACE inhibitors from hyperkalemia or renal insufficiency are likely to experience the same side effects with ARBs. In these cases, the combination of hydralazine and an oral nitrate should be considered. • ARBs should be considered in patients experiencing angioedema while on ACE inhibitors based on their underlying risk and with recognition that angioedema has been reported infrequently with ARBs. The combination of hydralazine and oral nitrates may be considered in such patients not tolerating ARB therapy. • A combination of hydralazine and an oral nitrate is recommended in African American patients with heart failure and reduced left ventricular ejection fraction (LVEF) who are on a standard regimen of an ACE inhibitor (or ARB) and a β-blocker. • A combination of hydralazine and an oral nitrate may be considered in non–African American patients with heart failure and reduced LVEF who are symptomatic despite optimization of standard therapy. • Administration of an aldosterone antagonist is recommended for patients with New York Heart Association (NYHA) class IV (or class III, previously class IV) heart failure from reduced LVEF (<35%) while receiving standard therapy, including diuretics. • Administration of an aldosterone antagonist should be considered in patients following an acute MI, with clinical heart failure signs and symptoms or history of diabetes mellitus, and an LVEF <40%. Patients should be on standard therapy, including an ACE inhibitor (or ARB) and a β-blocker. • The triple combination of an ACE inhibitor, an ARB, and an aldosterone antagonist is not recommended because of the high risk of hyperkalemia.

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	<u>Patients with hypertension and symptomatic left ventricular dysfunction with left ventricular dilation and low LVEF</u> • ACE inhibitors, ARBs, β-blockers, aldosterone inhibitors, and isosorbide dinitrate/hydralazine in various combinations (with a loop diuretic if needed) are recommended. • If blood pressure remains >130/80 mm Hg, a dihydropyridine calcium channel blocker (e.g., amlodipine or felodipine) may be considered or other antihypertensive medication doses increased. <u>Managing heart failure in special populations</u> • The combination of hydralazine/isosorbide dinitrate is recommended for African American women with moderate to severe heart failure symptoms who are on background neurohormonal inhibition. • A combination of hydralazine and isosorbide dinitrate is recommended as part of standard therapy in addition to β-blockers and ACE-inhibitors for African Americans with left ventricular systolic dysfunction and NYHA class II-IV heart failure. • As in all patients, but especially in the elderly, careful attention to volume status, the possibility of symptomatic cerebrovascular disease and the presence of postural hypotension are recommended during therapy with ACE inhibitors, β-blockers and diuretics. <u>Patients with heart failure and preserved LVEF</u> • ACE inhibitors or ARBs should be considered in this patient population. • ACE inhibitors should be considered in patients with heart failure and symptomatic atherosclerotic cardiovascular disease or diabetes and at least one other risk factor. ARBs may be used in patients who are intolerant to ACE inhibitors. • Beta-blocker treatment is recommended in patients with HF and preserved LVEF who have prior MI, hypertension, or AF. • Calcium channel blockers should be considered in patients with heart failure and preserved LVEF who have atrial fibrillation requiring ventricular rate control and intolerance to β-blockers (consider diltiazem or verapamil), symptom-limiting angina, or hypertension. • Diuretic therapy is recommended in all patients with heart failure and clinical evidence of volume overload, including those with preserved LVEF. • Treatment may begin with either a thiazide or loop diuretic. In more severe volume overload or if response to a thiazide is inadequate, treatment with a loop diuretic should be implemented. • Excessive diuresis, which may lead to orthostatic changes in blood pressure and worsening renal function, should be avoided. <u>Patients with heart failure and CAD</u> • Calcium channel blockers should be considered in patients who have angina despite optimization of β-blocker and nitrates. Amlodipine and felodipine are preferred in patients with decreased systolic function. <u>Patients with heart failure and hypertension</u> • Patients with left ventricular hypertrophy or left ventricular dysfunction without left ventricular dilation should be treated to a goal blood pressure of <130/80 mm Hg. Treatment with several drugs may be necessary, including an ACE inhibitor (or ARB), a diuretic and a β-blocker or calcium channel blocker. • Patients with asymptomatic left ventricular dysfunction and left ventricular dilation and a reduced ejection fraction should receive an ACE inhibitor and a β-blocker. If blood pressure remains elevated (>130/80 mm Hg), the addition of a diuretic is

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	recommended, followed by a calcium channel blocker or other antihypertensive agent. • If blood pressure remains >130/80 mm Hg, then the addition of a thiazide diuretic is recommended, followed by a dihydropyridine calcium channel blocker (e.g., amlodipine or felodipine) or other antihypertensive drugs. <u>Patients at risk for development of heart failure</u> • ACE inhibitors are recommended in patients who are at risk for the development of heart failure including patients with CAD, peripheral vascular disease, stroke, diabetes and another major risk factor, and patients with diabetes who smoke and have microalbuminuria. <u>Patients with asymptomatic heart failure and reduced LVEF</u> • ACE inhibitors are recommended in asymptomatic patients with reduced LVEF (<40%). • ARBs may be used in patients who are intolerant to ACE inhibitors. • Routine use of a combination of ACE inhibitors and ARBs is not recommended. • β-blocker therapy should be considered. <u>Patients with heart failure and ischemic heart disease</u> • ACE inhibitor therapy is recommended in all patients with either reduced or preserved LVEF after a MI. • Beta-blockers are recommended for the management of all patients with reduced LVEF or post-MI. • ACE inhibitor and β-blocker therapy should be initiated early (<48 hours) during hospitalization in hemodynamically stable patients who are post-MI with reduced LVEF or heart failure. • Calcium channel blockers may be considered in patients with HF who have angina despite the optimal use of β-blockers and nitrates. <u>Managing heart failure in the elderly, women and African Americans</u> • Standard regimens of ACE inhibitors and β-blockers are recommended in elderly patients with heart failure. • ACE inhibitor and β-blocker therapy are recommended in all women with heart failure and left ventricular systolic dysfunction. • ACE inhibitor and β-blocker therapy are recommended in all African American patients with heart failure and left ventricular systolic dysfunction. ARBs may be substituted in patients who are intolerant to ACE inhibitors. <u>Heart failure in patients with reduced ejection fraction</u> • ACE inhibitors are recommended in asymptomatic patients with reduced LVEF (<40%). • ARBs may be used in patients who are intolerant to ACE inhibitors. • β-blockers shown to be effective in clinical trials of patients with heart failure are recommended for patients with a LVEF ≤40%. • The combination of a β-blocker and an ACE inhibitor is recommended as routine therapy for asymptomatic patients with a LVEF ≤40%. The evidence is stronger in patients with a history of MI. • β-blocker therapy is recommended for patients with a recent decompensation of heart failure after optimization of volume status and successful discontinuation of intravenous diuretics and vasoactive drugs. Whenever possible, β-blocker therapy should be initiated in the hospital setting at a low dose prior to discharge of stable patients. • β-blocker therapy is recommended in the great majority of patients with heart failure and reduced LVEF, even if there is concurrent diabetes, chronic obstructive

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	pulmonary disease or peripheral vascular disease. Caution may be warranted in these patients. • It is recommended that β blockade be initiated at low doses and uptitrated gradually. • It is recommended that β-blocker therapy be continued in most patients experiencing a symptomatic exacerbation of heart failure during chronic maintenance treatment, unless they develop cardiogenic shock, refractory volume overload or symptomatic bradycardia. • The routine use of an ARB is not recommended in addition to an ACE inhibitor and a β-blocker in patients with a recent acute MI and reduced LVEF. • The addition of an ARB should be considered in patients with heart failure due to reduced LVEF who have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor and a β-blocker. • Administration of an aldosterone antagonist is recommended for patients with NYHA class IV (or class III, previously class IV) HF from reduced LVEF (<35%) while receiving standard therapy, including diuretics. • Diuretic therapy is recommended to restore and maintain normal volume status in patients with clinical evidence of fluid overload, generally manifested by congestive symptoms or signs of elevated filling pressures. Loop diuretics rather than thiazide-type diuretics are typically necessary to restore normal volume status in patients with heart failure. • The initial dose of diuretic may be increased as necessary to relieve congestion, and restoration of normal volume status may require multiple adjustments, especially in patients with severe fluid overload evidenced by massive edema or ascites. After a diuretic effect is achieved with loop diuretics (short acting), increasing administration frequency to twice or even three times/day will provide more diuresis with less physiologic perturbation than larger single doses. • Oral torsemide may be considered in patients in whom poor absorption of oral medication or erratic diuretic effect may be present. Particularly in patients with right-sided heart failure and refractory fluid retention despite high doses of other loop diuretics. • Intravenous administration of diuretics may be necessary to relieve congestion. • Diuretic refractoriness may represent patient nonadherence, a direct effect of diuretic use on the kidney or progression of underlying cardiac dysfunction. • Addition of chlorothiazide or metolazone, once or twice daily, to loop diuretics should be considered in patients with persistent fluid retention despite high dose loop diuretic therapy. Chronic daily use should be avoided if possible because of the potential for electrolyte shifts and volume depletion. These drugs may be used periodically (every other day or weekly) to optimize fluid management. Metolazone will generally be more potent and much longer acting in this setting and in patients with chronic renal insufficiency, so administration should be adjusted accordingly. Volume status and electrolytes must be monitored closely when multiple diuretics are used. • Careful observation for the development of side effects is recommended in patients treated with diuretics, especially when high doses or combination therapy are used. Patients should undergo routine laboratory studies and clinical examination as dictated by their clinical response. • Patients requiring diuretic therapy to treated fluid retention associated with heart failure generally require chronic treatment, although often at lower doses than those required initially to achieve diuresis. Decreasing or discontinuing therapy may be considered in patients experiencing significant improvement in clinical status and cardiac function or in those who successfully restrict dietary sodium intake. These patients may undergo cautious weaning of diuretic dose and frequency with careful observation for recurrent fluid retention. • Patients and caregivers should be given education on the early signs of fluid

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	retention and the plan for initial therapy.
	• Selected patients may be educated to adjust daily dose of diuretic in response to weight gain from fluid overload.
	
	<u>Evaluation and management of patients with acute decompensated heart failure</u>
	• Patients admitted with acute decompensated heart failure and evidence of fluid overload be treated initially with loop diuretics; usually given intravenously rather than orally. Ultrafiltration may be considered in lieu of diuretics.
	• Diuretics should be administered at doses needed to produce a rate of diuresis sufficient to achieve optimal volume status with relief of signs and symptoms of congestion, without inducing an excessively rapid reduction in intravascular volume or serum electrolytes.
	• Monitoring of daily weights, intake and output is recommended to assess clinical efficacy of diuretic therapy.
	• Careful observation for development of a variety of side effects, including renal dysfunction, electrolyte abnormalities, symptomatic hypotension and gout is recommended in patients treated with diuretics, especially when high doses or combination therapy is used.
	• Careful observation for the development of renal dysfunction is recommended in patients treated with diuretics. Patients with moderate to severe renal dysfunction and evidence of fluid retention should continue to be treated with diuretics. In the presence of severe fluid overload, renal dysfunction may improve with diuresis.
	• When congestion fails to improve in response to diuretic therapy, the following options should be considered:
	  ○ Re-evaluating the presence/absence of congestion.
	  ○ Sodium and fluid restriction.
	  ○ Increasing doses of loop diuretic.
	  ○ Continuous infusion of a loop diuretic.
	  ○ Addition of a second type of diuretic orally (metolazone or spironolactone) or intravenously (chlorothiazide).
	  ○ Ultrafiltration may be considered as well.

European Society of Cardiology: **Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (2016)**[36]	<u>Pharmacological treatments indicated in patients with symptomatic (NYHA Class II-IV) heart failure with reduced ejection fraction</u> • An ACE inhibitor is recommended, in addition to a beat-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death. • A mineralocorticoid receptor antagonist 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. • Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion. • 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. • 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).

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	• 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. • 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 heart failure with preserved ejection fraction and heart failure with mid-range ejection fraction</u> • It is recommended to screen patients with HFpEF or HFmrEF (mid-range) 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 or HFmrEF in order to alleviate symptoms and signs. <u>Recommendations for initial management of a rapid ventricular rate in patients with heart failure and atrial fibrillation in the acute or chronic setting</u> • Urgent electrical cardioversion is recommended if AF is thought to be contributing to the patient's hemodynamic compromise in order to improve the patient clinical condition. • For patients in NYHA Class IV, in addition to treatment for acute HF, an intravenous bolus of amiodarone or, in digoxin-naïve patients, an intravenous bolus of digoxin should be considered to reduce the ventricular rate. • For patients in NYHA Class I–III, a β-blocker, usually given orally, is safe and therefore is recommended as first-line treatment to control ventricular rate, provided the patient is euvolemic. • For patients in NYHA Class I–III, digoxin should be considered when ventricular rate remains high despite β-blockers or when β-blockers are not tolerated or contraindicated. • Treatment with dronedarone to improve ventricular rate control is not recommended due to safety concerns. <u>Recommendations for cardiac imaging in patients with suspected or established heart failure</u> • Transthoracic Echocardiogram (TTE) is recommended for the assessment of myocardial structure and function in subjects with suspected HF in order to establish a diagnosis of HFrEF, HFmrEF, or HFpEF. • TTE is recommended for the assessment of LVEF in order to identify patients with HF who would be suitable for evidence-based pharmacological and device treatment recommended for HFrEF.

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	Recommendations aiming to prevent or delay the development of overt heart failure or prevent death before the onset of symptoms • Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life. • ACE inhibitor is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction in order to prevent or delay the onset of HF and prolong life. • Beta-blocker is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction, in order to prevent or delay the onset of HF and prolong life. Pharmacological treatments indicated in patients with symptomatic 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 β-blocker is recommended, in addition to an ACE inhibitor, for patients with stable, symptomatic HFrEF to reduce the risk of HF hospitalization and death. • A mineralocorticoid receptor antagonist 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. Other pharmacological treatments recommended in selected patients with symptomatic heart failure with reduced ejection fraction • Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion. • 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. Treatments (or combinations of treatments) that may cause harm in patients with symptomatic (New York Heart Association Class II–IV) heart failure with reduced ejection fraction • Diltiazem or verapamil are not recommended in patients with HFrEF, as they increase the risk of HF worsening and HF hospitalization. • The addition of an ARB (or a renin inhibitor) to the combination of an ACE inhibitor and a mineralocorticoid receptor antagonist is not recommended in patients with HF, because of the increased risk of renal dysfunction and hyperkalemia. Not-recommended treatments of co-morbidities in patients with heart failure • Thiazolidinediones (glitazones) are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization. • NSAIDs or COX-2 inhibitors are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization. Recommendations for the 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. • In patients with new-onset AHF or those with chronic, decompensated HF not receiving oral diuretics the initial recommended dose should be 20 to 40 mg intravenous furosemide (or equivalent); for those on chronic diuretic therapy, initial

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	intravenous dose should be at least equivalent to oral dose. • It is recommended to give diuretics either as intermittent boluses or a continuous infusion, and the dose and duration should be adjusted according to the patients' symptoms and clinical status. • Inotropic agents are not recommended unless the patient is symptomatically hypotensive or hypoperfused because of safety concern.
American Heart Association/ American College of Cardiology/ Heart Rhythm Society: **Guideline for the Management of Patients with Atrial Fibrillation (2014)**[37]	Recommendations for risk-based antithrombotic therapy: Class I • In patients with atrial fibrillation (AF), antithrombotic therapy should be individualized based on shared decision-making after discussion of the absolute and relative risks of stroke, bleeding and the patient's values and preferences (Level of Evidence: C). • Selection of antithrombotic therapy should be based on the risk of thromboembolism irrespective of whether the AF patter is paroxysmal, persistent, or permanent (Level of Evidence: B). • In patients with nonvalvular AF, the CHA_2DS_2-VASc score is recommended for assessment of stroke risk (Level of Evidence: B). • For patients with AF who have mechanical heart valves, warfarin is recommended and the target international normalized ratio (INR) should be based on type and location of the prosthesis (Level of Evidence: B). • For patients with nonvalvular AF with prior stroke, TIA, or a CHA_2DS_2-VASc score ≥2, oral anticoagulants are recommended. Options include warfarin (INR 2.0 to 3.0) (Level of Evidence: A), dabigatran, rivaroxaban, or apixaban (Level of Evidence: B). • For patients treated with warfarin, the INR should be determined at least weekly during initiation of antithrombotic therapy and at least monthly when anticoagulation (INR in range) is stable (Level of Evidence: A) • For patients with nonvalvular AF unable to maintain a therapeutic INR level with warfarin, use of a direct thrombin or factor Xa inhibitor is recommended (Level of Evidence: C). • Re-evaluation of the need for and choice of antithrombotic therapy at periodic intervals is recommended to reassess stroke and bleeding risks (Level of Evidence: C). • Bridging therapy with UFH or LMWH is recommended for patients with AF and a mechanical heart valve undergoing procedures that require interruption of warfarin. Decisions regarding bridging therapy should balance the risks of stroke and bleeding (Level of Evidence: C). • For patients with AF without mechanical heart valves who require interruption of warfarin or newer anticoagulants for procedures, decisions about bridging therapy (LMWH or UFH) should balance the risks of stroke and bleeding and the duration of time a patient will not be anticoagulated (Level of Evidence: C). • Renal function should be evaluated prior to initiation of direct thrombin or factor Xa inhibitors and should be re-evaluated when clinically indicated and at least annually (Level of Evidence: B). • For patients with atrial flutter, antithrombotic therapy is recommended according to the same risk profile used for AF (Level of Evidence: C). Class IIa • For patients with nonvalvular AF and a CHA_2DS_2-VASc score of 0, it is reasonable to omit antithrombotic therapy (Level of Evidence: B). • For patients with nonvalvular AF with a CHA_2DS_2-VASc score of ≥2 and who have end-stage chronic kidney disease (creatine clearance <15 mL/min) or who are on hemodialysis, it is reasonable to prescribe warfarin (INR 2.0 to 3.0) for oral anticoagulation (Level of Evidence: B). Class IIb

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	• For patients with nonvalvular AF and a CHA_2DS_2-VASc score of 1, no antithrombotic therapy or treatment with an oral anticoagulant or aspirin may be considered (Level of Evidence: C). • For patients with nonvalvular AF and moderate-to-severe chronic kidney disease with a CHA_2DS_2-VASc score of ≥2, treatment with reduced doses of direct thrombin or factor Xa inhibitors may be considered (e.g., dabigatran, rivaroxaban, or apixaban), but safety and efficacy have not been established (Level of Evidence: C). • In patients with AF undergoing PCI, bare-metal stents may be considered to minimize the required duration of dual antiplatelet therapy. Anticoagulation may be interrupted at the time of the procedure to reduce the risk of bleeding ant the site of peripheral arterial puncture (Level of Evidence: C). • Following coronary revascularization (percutaneous or surgical) in patients with AF and a CHA_2DS_2-VASc score of ≥2, it may be reasonable to use clopidogrel (75 mg once daily) concurrently with oral anticoagulants but without aspirin (Level of Evidence: B). Class III: No Benefit • The direct thrombin inhibitor, dabigatran, and the factor Xa inhibitor, rivaroxaban, are not recommended in patients with AF and end-stage chronic kidney disease or on hemodialysis because of the lack of evidence from clinical trials regarding the balance of risks and benefits (Level of Evidence: C). Class III: Harm • The direct thrombin inhibitor, dabigatran, should not be used in patients with AF and a mechanical heart valve (Level of Evidence: B). <u>Recommendations for rate control:</u> Class I • Control of the ventricular rate using a β-blocker or nondihydropyridine (non-DHP) calcium channel blocker (CCB) is recommended for patients with paroxysmal, persistent, or permanent AF (Level of Evidence: B). • Intravenous administration of a β-blocker or non-DHP CCB is recommended to slow the ventricular heart rate in the acute setting in patients without pre-excitation. In hemodynamically unstable patients, electrical cardioversion is indicated (Level of Evidence: B). • In patients who experience AF-related symptoms during activity, the adequacy of heart rate control should be assessed during exertion, adjusting pharmacological treatment as necessary to keep the ventricular rate within the physiological range (Level of Evidence: C). Class IIa • A heart rate control (resting heart rate <80 beats per minute [bpm]) strategy is reasonable for symptomatic management of AF (Level of Evidence: B). • Intravenous amiodarone can be useful for rate control in critically ill patients without pre-excitation (Level of Evidence: B). • Atrioventricular (AV) nodal ablation with permanent ventricular pacing is reasonable to control heart rate when pharmacological therapy is inadequate and rhythm control is not achievable (Level of Evidence: B). Class IIb • A lenient rate-control strategy (resting heart rate <110 bpm) may be reasonable as long as patients remain asymptomatic and left ventricular systolic function is preserved (Level of Evidence: B). • Oral amiodarone may be useful for ventricular rate control when other measures are unsuccessful or contraindicated (Level of Evidence: C). Class III: Harm • AV nodal ablation with permanent ventricular pacing should not be performed to improve rate control without prior attempts to achieve rate control with

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	medications (Level of Evidence: C). • Non-DHP CCBs should not be used in patients with decompensated HF as these may lead to further hemodynamic compromise (Level of Evidence: C). • In patients with pre-excitation and AF, digoxin, non-DHP CCBs, or intravenous amiodarone should not be administered as they may increase the ventricular response and may result in ventricular fibrillation. (Level of Evidence: B). • Dronedarone should not be used to control the ventricular rate in patients with permanent AF as it increases the risk of the combined endpoint of stroke, myocardial infarction, systemic embolism, or cardiovascular death (Level of Evidence: B). <u>Recommendations for Thromboembolism Prevention</u>: Class I • For patients with AF or atrial flutter of 48-hour duration or longer, or when the duration of AF is unknown, anticoagulation with warfarin (INR 2.0 to 3.0) is recommended for at least three weeks prior to and four weeks after cardioversion, regardless of the CHA_2DS_2-VASc score and the method used to restore sinus rhythm (Level of Evidence: B). • For patients with AF or atrial flutter of more than 48 hours duration that requires immediate cardioversion for hemodynamic instability, anticoagulation should be initiated as soon as possible and continued for at least four weeks after cardioversion unless contraindicated (Level of Evidence: C). • For patients with AF or atrial flutter of less than 48-hour duration and with high risk stroke, intravenous heparin or LMWH, or administration of a factor Xa or direct thrombin inhibitor, is recommended as soon as possible before or immediately after cardioversion, followed by long-term anticoagulation therapy (Level of Evidence: C). • Following cardioversion for AF of any duration, the decision regarding long-term anticoagulation therapy should be based on the thromboembolic risk profile (Level of Evidence: C). Class IIa • For patients with AF or atrial flutter of 48-hour duration or longer or of unknown duration who have not been anticoagulated for the preceding three weeks, it is reasonable to perform a TEE prior to cardioversion and proceed with cardioversion if no LA thrombus is identified, including in the LAA, provided that anticoagulation is achieved before TEE and maintained after cardioversion for at least four weeks (Level of Evidence: B). • For patients with AF or atrial flutter of 48-hour duration or longer, or when the duration of AF is unknown, anticoagulation with dabigatran, rivaroxaban, or apixaban is reasonable for at least three weeks prior to and four weeks after cardioversion (Level of Evidence: C). Class IIb • For patients with AF or atrial flutter of less than 48-hour duration who are at low thromboembolic risk, anticoagulation (heparin, LMWH, or a new oral anticoagulant) or no antithrombotic therapy may be considered for cardioversion, without the need for post cardioversion oral anticoagulation (Level of Evidence: C). <u>Recommendations for pharmacological cardioversion</u> Class I • Flecainide, dofetilide, propafenone, and intravenous ibutilide are useful for pharmacological cardioversion of AF or atrial flutter, provided contraindications to the selected drug are absent (Level of Evidence: A). Class IIa • Administration of oral amiodarone is a reasonable option for pharmacological

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	cardioversion of AF (Level of Evidence: A).
	• Propafenone or flecainide ("pill-in-the-pocket") in addition to a β-blocker or non-DHP CCB is reasonable to terminate AF outside the hospital once this treatment has been observed to be safe in a monitored setting for selected patients (Level of Evidence: B).
	Class III: Harm
	• Dofetilide therapy should not be initiated out of hospital because of the risk of excessive QT prolongation that can cause torsades de pointes (Level of Evidence: B).
	
	<u>Recommendations for antiarrhythmic drugs to maintain sinus rhythm</u>
	Class I
	• Before initiating antiarrhythmic drug therapy, treatment of precipitating or reversible causes of AF is recommended (Level of Evidence: C).
	• The following antiarrhythmic drugs are recommended in patients with AF to maintain sinus rhythm, depending on underlying heart disease and comorbidities (Level of Evidence: A):
	  o Amiodarone
	  o Dofetilide
	  o Dronedarone
	  o Flecainide
	  o Propafenone
	  o Sotalol
	• The risks of the antiarrhythmic drug, including proarrhythmia, should be considered before initiating therapy with each drug (Level of Evidence: C).
	• Because of its potential toxicities, amiodarone should only be used after consideration of risks and when other agents have failed or are contraindicated (Level of Evidence: C).
	Class IIa
	• A rhythm-control strategy with pharmacological therapy can be useful in patients with AF for the treatment of tachycardia-induced cardiomyopathy (Level of Evidence: C).
	Class IIb
	• It may be reasonable to continue current antiarrhythmic drug therapy in the setting of infrequent, well-tolerated recurrences of AF when the drug has reduced the frequency or symptoms of AF (Level of Evidence: C).
	Class III: Harm
	• Antiarrhythmic drugs for rhythm control should not be continued when AF becomes permanent (Level of Evidence: C), including dronedarone (Level of Evidence: B).
	• Dronedarone should not be used for treatment of AF in patients with New York Heart Association class III and IV HF or patients who have had an episode of decompensated HF in the past 4 weeks. (Level of Evidence: B).
	
	<u>Upstream therapy</u>
	Class IIa
	• An angiotensin-converting enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB) is reasonable for primary prevention of new-onset AF in patients with HF with reduced left ventricular ejection fraction (Level of Evidence: B).
	Class IIb
	• Therapy with an ACE inhibitor or ARB may be considered for primary prevention of new-onset AF in the setting of hypertension (Level of Evidence: B).
	• Statin therapy may be reasonable for primary prevention of new-onset AF after coronary artery surgery (Level of Evidence: A).
	Class III: No Benefit

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	• Therapy with an ACE inhibitor, ARB, or statin is not beneficial for primary prevention of AF in patients without cardiovascular disease (Level of Evidence: B).

National Institute for Health and Clinical Excellence: **Atrial Fibrillation: The Management of Atrial Fibrillation (2014)**[38]	<u>Interventions to prevent stroke</u>
	• Do not offer stroke prevention to people aged <65 years with atrial fibrillation (AF) and no risk factors other than their sex (that is, very low risk of stroke equating to CHA_2DS_2-VASc score of 0 for men or 1 for women).
	• Consider anticoagulation for men with a CHA_2DS_2-VASc score of 1. Take the bleeding risk into account.
	• Offer anticoagulation to people with a CHA_2DS_2-VASc score of 2 or above, taking bleeding risk into account.
	• Discuss the options for anticoagulation with the person and base the choice on their clinical features and preferences.
	• Apixaban
	  o Apixaban is recommended as an option for preventing stroke and systemic embolism within its marketing authorization, that is, in people with nonvalvular atrial fibrillation with one or more risk factors such as:
	  ▪ Prior stroke of transient ischemic attack (TIA).
	  ▪ Age 75 years or older.
	  ▪ Hypertension.
	  ▪ Diabetes mellitus.
	  ▪ Symptomatic heart failure.
	• Dabigatran etexilate
	  o Dabigatran etexilate is recommended as an option for the prevention of stroke and systemic embolism within its licensed indication, that is, in people with nonvalvular atrial fibrillation with one or more of the following risk factors:
	  ▪ Previous stroke, TIA, or systemic embolism.
	  ▪ Left ventricular ejection fraction (LVEF) <40%.
	  ▪ Symptomatic heart failure (HF) of New York Heart Association (NYHA) class 2 or above.
	  ▪ Age 75 years or older.
	  ▪ Age 65 years or older with one of the following: diabetes mellitus, coronary artery disease, or hypertension.
	• Rivaroxaban
	  o Rivaroxaban is recommended as an option for the prevention of stroke and systemic embolism within its licensed indication, that is, in people with nonvalvular AF with one or more risk factors such as:
	  ▪ Congestive heart failure.
	  ▪ Hypertension.
	  ▪ Age 75 years or older.
	  ▪ Diabetes mellitus.
	  ▪ Prior stroke or TIA.
	• The decision about whether to start treatment with a new oral anticoagulant should be made after an informed discussion between the clinician and the person about the risks and benefits of the agent compared with the alternatives, including warfarin. For people who are taking warfarin, the potential risks and benefits of switching to a different oral agent should be considered in light of their level of international normalized ratio (INR) control.
	
	<u>Assessing anticoagulation control with vitamin K antagonists</u>
	• Calculate the person's time in therapeutic range (TTR) at each visit. When calculating TTR:
	  o Use a validated method of measurement such as the Rosendaal method for computer-assisted dosing or proportion of tests in range for manual dosing.
	  o Exclude measurements taken during the first six weeks of treatment.
	  o Calculate TTR over a maintenance period of at least six months.

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	• Reassess anticoagulation for a person with poor anticoagulation control shown by any of the following:
	  o Two INR values higher than 5 or one INR value higher than 8 within the past six months.
	  o Two INR values less than 1.5 within the past six months.
	  o TTR <65%.
	• When assessing anticoagulation, take into account and if possible address the following factors that may contribute to poor anticoagulation control: Cognitive function, adherence, illness, drug interactions, and lifestyle factors including diet and alcohol consumption.
	• If poor anticoagulation control cannot be improved, evaluate the risks and benefits of alternative stroke prevention strategies and discuss these with the person.
	
	<u>When to offer rate and rhythm control</u>
	• Offer rate control as the first-line strategy to people with AF, except in people whose AF has a reversible cause, who have HF thought to be primarily caused by AF, with new-onset AF, with atrial flutter whose condition is considered suitable for an ablation strategy to restore sinus rhythm, and for whom a rhythm control strategy would be more suitable based on clinical judgement.
	
	<u>Rate control</u>
	• Offer either a standard β-blocker (that is, a β-blocker other than sotalol) or a rate-limiting calcium channel blocker (CCB) as initial monotherapy to people with AF who need drug treatment as part of a rate control strategy. Base the choice of drug on the person's symptoms, heart rate, comorbidities, and preferences when considering drug treatment.
	• Consider digoxin monotherapy for people with non-paroxysmal AF only if they are sedentary.
	• 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.
	
	<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.
	• 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.

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	▪ Previous TIA, stroke, or systemic embolism. ▪ Left atrial diameter of 50 mm or greater, OR ▪ Age ≥70 years, AND ○ Who do not have left ventricular systolic dysfunction, AND ○ Who do not have a history of, or current, HF. • 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 HF. • 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.
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)**[39]	Recommended prevention strategies for all postoperative atrial fibrillation (POAF) patients • 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. Recommended prevention strategies for intermediate to high-risk POAF patients • 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. Rate control recommendations for patients with new onset POAF • 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.

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	• 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. Recommendations for the use of antiarrhythmic drugs for pharmacologic cardioversion of POAF • 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 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. Recommendations for prevention of thromboembolism for patients with stable atrial fibrillation/flutter undergoing direct current cardioversion • 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,

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	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. Management of anticoagulation for new onset POAF • 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 (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 (2006)**[40]	Note: There is a European update to the American College of Cardiology (ACC)/American Heart Association (AHA)/ESC 2006 Guidelines for management of patients with ventricular arrhythmias (VA) and the prevention of sudden cardiac death (SCD). The new 2015 ESC Guidelines Committee focus on the prevention of SCD. Drug therapy for ventricular arrhythmias • β-blockers are currently the mainstay of pharmacologic therapy for the treatment of arrhythmias, due to their safety profile and effectiveness. • Other than β-blockers, alternative antiarrhythmic agents currently available have not been proven effective in the primary management of patients with life-threatening ventricular arrhythmias or in the prevention of sudden cardiac death. • For patients that are arrhythmia-prone, antiarrhythmic agents may be effective as adjunctive therapy in particular situations. • Caution should be used when any antiarrhythmic agent is used for therapy, as there are many side effects associated with these agents. • β-blockers, or alternatively, amiodarone or sotalol, may be used in patients with ventricular tachycardia who do not meet criteria for an implantable cardioverter-defibrillator. • Sotalol or, alternatively the combination of β-blockers and amiodarone, may be used in patients with implantable cardioverter-defibrillators who have recurrent ventricular tachycardia/ventricular fibrillation with frequent appropriate implantable cardioverter-defibrillator firing. Ventricular arrhythmia and sudden cardiac death related to specific pathology Left ventricular dysfunction due to prior MI: • Amiodarone, often in combination with β-blockers, can be useful for patients with left ventricular dysfunction due to prior MI and symptoms due to ventricular tachycardia unresponsive to β-blocking agents.

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	• Sotalol is reasonable therapy to reduce symptoms resulting from ventricular tachycardia for patients with left ventricular dysfunction due to prior MI unresponsive to β-blocking agents. • Alternative therapies to the implantable cardioverter-defibrillator to improve symptoms due to frequent episodes of sustained ventricular tachycardia or ventricular fibrillation in patients with left ventricular dysfunction due to prior MI include agents such as amiodarone or sotalol. • To reduce symptoms in patients due to recurrent hemodynamically stable ventricular tachycardia with left ventricular dysfunction due to prior MI and who cannot or refuse to have an implantable cardioverter-defibrillator implanted, amiodarone may be used as an alternative therapy. • To improve symptoms in patients with left ventricular dysfunction due to prior MI and recurrent hemodynamically stable ventricular tachycardia whose LVEF is >40% and an implantable cardioverter-defibrillator is not appropriate, amiodarone may be considered an alternative treatment option. • In patients with left ventricular dysfunction due to prior MI where an implantable cardioverter-defibrillator is indicated but is not appropriate or desired by the patient, amiodarone may be considered an alternative treatment option. • Prophylactic antiarrhythmic drug therapy is not indicated to reduce mortality in patients with asymptomatic nonsustained ventricular arrhythmias. • Class Ic antiarrhythmic agents are not recommended in patients with a past history of MI. <u>Congenital heart disease</u>: • Prophylactic antiarrhythmic therapy is not indicated for asymptomatic patients with congenital heart disease and isolated premature ventricular contractions. <u>Metabolic and inflammatory conditions</u>: • Antiarrhythmic therapy can be useful in patients with symptomatic non-sustained ventricular tachycardia or sustained ventricular tachycardia during the acute phase of myocarditis. <u>Pericardial disease</u>: • Prophylactic antiarrhythmic therapy generally is not indicated for primary prevention of sudden cardiac death in patients with pulmonary arterial hypertension or other pulmonary conditions. <u>Ventricular arrhythmias associated with cardiomyopathies</u> Dilated cardiomyopathy (nonischemic): • Amiodarone may be considered for sustained ventricular tachycardia or ventricular fibrillation in patients with nonischemic dilated cardiomyopathy. <u>Hypertrophic cardiomyopathy</u> • Amiodarone therapy can be effective for treatment in patients with hypertrophic cardiomyopathy with a history of sustained ventricular tachycardia and/or ventricular fibrillation when implantable cardioverter-defibrillator is not feasible. • Amiodarone may be considered for primary prophylaxis against sudden cardiac death in patients with hypertrophic cardiomyopathy who have one or more major risk factor for sudden cardiac death, if implantable cardioverter-defibrillator implantation is not feasible. <u>Arrhythmogenic right ventricular cardiomyopathy</u> • Amiodarone or sotalol can be effective for treatment of sustained ventricular tachycardia or ventricular fibrillation in patients with arrhythmogenic right ventricular cardiomyopathy when implantable cardioverter-defibrillator

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	implantation is not feasible. <u>Heart failure</u> • Amiodarone, sotalol and/or other β-blockers are recommended pharmacological adjuncts to implantable cardioverter-defibrillator therapy to suppress symptomatic ventricular tachyarrhythmias (both sustained and nonsustained) in otherwise optimally treated patients with heart failure. • Amiodarone is indicated for the suppression of acute hemodynamically compromising ventricular or supraventricular tachyarrhythmias when cardioversion and/or correction of reversible causes have failed to terminate the arrhythmia or prevent its early recurrence. • Amiodarone, sotalol, and/or β-blockers may be considered as pharmacological alternatives to implantable cardioverter-defibrillator therapy to suppress symptomatic ventricular tachyarrhythmias (both sustained and nonsustained) in optimally treated patients with heart failure for whom implantable cardioverter-defibrillator therapy is not feasible. <u>Genetic arrhythmia syndromes</u> Long QT syndrome: • β-blockers are recommended for patients with a long QT syndrome clinical diagnosis (i.e., in the presence of prolonged QT interval). • Implantation of an implantable cardioverter-defibrillator along with use of β-blockers is recommended for long QT syndrome patients with previous cardiac arrest and who have reasonable expectation of survival with a good functional status for more than one year. • β-blockers can be effective to reduce sudden cardiac death in patients with a molecular long QT syndrome analysis and normal QT interval. • Implantation of an implantable cardioverter-defibrillator with continued use of β-blockers can be effective to reduce sudden cardiac death in long QT syndrome patients experiencing syncope and/or ventricular tachycardia while receiving β-blockers and who have reasonable expectation of survival with a good functional status for more than one year. <u>Short QT syndrome and Brugada syndrome</u>: • Quinidine might be reasonable for the treatment of electrical storm in patients with Brugada syndrome. <u>Catecholaminergic polymorphic ventricular tachycardia</u>: • β-blockers are indicated for patients who are clinically diagnosed with catecholaminergic polymorphic ventricular tachycardia on the basis of the presence of spontaneous or documented stress-induced ventricular arrhythmias. • β-blockers can be effective in patients without clinical manifestations when the diagnosis of catecholaminergic polymorphic ventricular tachycardia is established during childhood based on genetic analysis. • β-blockers may be considered for patients with catecholaminergic polymorphic ventricular tachycardia who were genetically diagnosed in adulthood and never manifested clinical symptoms of tachyarrhythmias. <u>Arrhythmias in structurally normal hearts</u> Idiopathic ventricular tachycardia: • Drug therapy with β-blockers and/or calcium channel blockers can be useful in patients with structurally normal hearts with symptomatic ventricular tachycardia arising from the right ventricle. <u>Ventricular arrhythmias and sudden cardiac death related to specific populations</u>

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	Pregnancy: • In pregnant women with the long QT syndrome who have had symptoms, it is beneficial to continue β-blocker medications throughout pregnancy and afterward, unless there are definite contraindications. Elderly: • The dosing and titration schedule of antiarrhythmic drugs prescribed to elderly patients should be adjusted to the altered pharmacokinetics of such patients.
European Society of Cardiology: **Guidelines on diagnosis and management of hypertrophic cardiomyopathy (2014)**[41]	• Patients with symptomatic left ventricular outflow tract obstruction should be treated initially with non-vasodilating β-blockers titrated to maximum tolerable dose. • If β-blockers alone are ineffective, disopyramide titrated to a maximum tolerated dose (usually 400 to 600 mg/day) may be added. • Verapamil can be used when β-blockers are contraindicated or ineffective, but close monitoring is required in patients with severe obstruction (≥100 mmHg) or elevated pulmonary artery systolic pressures, as it can provoke pulmonary edema. • Nifedipine and other dihydropyridine calcium antagonists are not recommended. • Low-dose loop or thiazide diuretics may be used cautiously to improve dyspnea, but it is important to avoid hypovolemia. • In patients without left ventricular outflow tract obstruction, An ACE inhibitor (or ARB if ACE inhibitor not tolerated) should be considered, in addition to a ß-blocker, for patients who have an LVEF <50%, to reduce the risks of HF hospitalization and premature death.
Eighth Joint National Committee (JNC 8): **2014 Evidence-based Guideline for the Management of High Blood Pressure in Adults (2014)**[42]	• 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.

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	• 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.
American Society of Hypertension/ International Society of Hypertension: **Clinical Practice Guidelines for the Management of Hypertension in the Community (2014)**[43]	Nonpharmacologic treatment • In patients with hypertension that is no more severe than stage one and is not associated with evidence of abnormal cardiovascular findings or other cardiovascular risks, six to 12 months of lifestyle changes can be attempted in the hope that they may be sufficiently effective to make it unnecessary to use medicines. • It may be prudent to start treatment with drugs sooner if it is clear that the blood pressure is not responding to the lifestyle methods or if other risk factors appear. • Weight loss: In patients who are overweight or obese, weight loss is helpful in treating hypertension, diabetes, and lipid disorders. • Salt reduction: Reduction of salt intake is recommended because it can reduce blood pressure and decrease the need for medications in patients who are "salt sensitive." • Exercise: Regular aerobic exercise can help reduce blood pressure. • Alcohol consumption: Up to two drinks a day can be helpful in protecting against cardiovascular events, but greater amounts of alcohol can raise blood pressure and should therefore be discouraged. In women, alcohol should be limited to one drink a day. • Cigarette smoking: Stopping smoking will not reduce blood pressure, but since smoking by itself is such a major cardiovascular risk factor, patients must be strongly urged to discontinue this habit. Drug treatment of hypertension • Treatment with drugs should be started in patients with blood pressures >140/90 mm Hg in whom lifestyle treatments have not been effective. • In patients with stage two hypertension (blood pressure ≥160/100 mm Hg), drug treatment should be started immediately after diagnosis, usually with a two-drug combination, without waiting to see the effects of lifestyle changes. • For patients older than 80 years, the suggested threshold for starting treatment is at levels ≥150/90 mm Hg. Thus, the target of treatment should be <140/90 mm Hg for most patients but <150/90 mm Hg for older patients (unless these patients have chronic kidney disease or diabetes, when <140/90 mm Hg can be considered). • Most patients will require more than one drug to achieve control of their blood pressure. • In general, increase the dose of drugs or add new drugs at approximately two to three week intervals. This frequency can be faster or slower depending on the judgment of the practitioner. In general, the initial doses of drugs chosen should be at least half of the maximum dose so that only one dose adjustment is required thereafter. It is generally anticipated that most patients should reach an effective treatment regimen, whether one, two, or three drugs, within six to eight weeks. • Choice of drugs should be influenced by the age, ethnicity/race, and other clinical characteristics of the patient. • The choice of drugs will also be influenced by other conditions (e.g., diabetes and coronary disease) associated with the hypertension. Pregnancy also influences drug choice. • Long-acting drugs that need to be taken only once daily are preferred to shorter-acting drugs that require multiple doses because patients are more likely to follow a simple treatment regimen. • This guideline only makes recommendations for drug classes, not individual agents. There is an assumption, unless otherwise stated, that all drugs in a class are similar to each other.

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	• Drug selectin when hypertension is the only or main concern: ○ For black patients of all ages, use calcium channel blocker (CCB) or thiazide diuretic as first drug, then add angiotensin receptor blocker (ARB) or angiotensin-converting enzyme (ACE) inhibitor if needed. ○ For white and other non-black patients <60 years of age, use ARB or ACE inhibitor as first drug, then add CCB or thiazide diuretic if needed. ○ For white and other non-black patients ≥60 years of age, use CCB or thiazide diuretic as first drug, then add ARB or ACE inhibitor if needed. • Drug selection when hypertension is associated with other conditions: ○ For patients with hypertension and diabetes, use ARB or ACE inhibitor as first drug (note, in black patients it is acceptable to start with a CCB or thiazide), then add CCB or thiazide diuretic (unless starting on CCB or thiazide in black patients) if needed. ○ For patients with hypertension and chronic kidney disease, use ARB or ACE inhibitor as first drug, then add CCB or thiazide diuretic if needed. ○ For patients with hypertension and clinical coronary artery disease, use β-blocker plus ARB or ACE inhibitor as first drugs, then add CCB or thiazide diuretic if needed. ○ For patients with hypertension and stroke history, use ACE inhibitor or ARB as first drug, then add thiazide diuretic or CCB if needed. • For patients with hypertension and heart failure, patients with h symptomatic heart failure should usually receive an ARB or ACE inhibitor plus β-blocker plus diuretic plus spironolactone regardless of blood pressure. A dihydropyridine CCB can be added if needed for blood pressure control.
Hypertension Canada: **2017 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults (2017)[44]**	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. 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

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	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. Guidelines for individuals 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

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	• 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.
	
	<u>Treatment of hypertension in association with stroke</u>
	• BP management in acute ischemic stroke (onset to 72 hours)
	  ○ For patients with ischemic stroke not eligible for thrombolytic therapy, treatment of hypertension in the setting of acute ischemic stroke or transient ischemic attack should not be routinely undertaken. Extreme BP increases (e.g., SBP >220 mmHg or DBP >120 mmHg) may be treated to reduce the BP by approximately 15%, and not more than 25%, over the first 24 hours with gradual reduction thereafter. Avoid excessive lowering of BP because this might exacerbate existing ischemia or might induce ischemia, particularly in the setting of intracranial arterial occlusion or extracranial carotid or vertebral artery occlusion. Pharmacological agents and routes of administration should be chosen to avoid precipitous decreases in BP.
	  ○ For patients with ischemic stroke eligible for thrombolytic therapy, very high BP (>185/110 mmHg) should be treated concurrently in patients receiving thrombolytic therapy for acute ischemic stroke to reduce the risk of secondary intracranial hemorrhage.
	• 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)
	  ○ For patients with intracerebral hemorrhage (ICH) in the hyperacute phase (in the first 24 hours) SBP lowering to <140 mmHg should be avoided because of an absence of benefit (relative to a target of <180 mmHg) and some suggestion of harm.
	
	<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

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	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 • For patients with nondiabetic chronic kidney disease, target BP is <140/90 mmHg. • For patients with hypertension and proteinuric chronic kidney disease (urinary protein >500 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. • Thiazide/thiazide-like diuretics are recommended as additive antihypertensive therapy. For patients with chronic kidney disease and volume overload, loop diuretics are an alternative. • 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. • In patients with hypertension attributable to FMD-related renal artery stenosis, revascularization should be considered. • 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 2 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. Combination therapy using two first-line agents may also be considered as initial treatment of hypertension if SBP is 20 mmHg greater than target or if DBP is 10 mmHg greater than target. However, caution should be exercised in patients in whom a substantial decrease in BP is more likely or poorly tolerated (e.g., elderly patients and patients with autonomic neuropathy). • 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.
European Society of Hypertension/European Society of	The 2013 guidelines on hypertension of the European Society of Hypertension and the European Society of Cardiology follow the guidelines jointly issued by the two societies in 2003 and 2007.

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Cardiology: **2013 Guidelines for the management of arterial hypertension (2013)[45]**	<u>Treatment strategies and choice of antihypertensive drugs</u> • Diuretics (including thiazides, chlorthalidone, and indapamide), β-blockers, calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) are all suitable for the initiation and maintenance of antihypertensive treatment, either as monotherapy or in some combinations. • Some agents should be considered as the preferential choice in specific conditions because used in trials in those conditions or because of greater effectiveness in specific types of organ damage. • Initiation of antihypertensive therapy with a two-drug combination may be considered in patients with markedly high baseline blood pressure (BP) or at high cardiovascular (CV) risk. • The combination of two antagonists of the renin-angiotensin system (RAS) is not recommended and should be discouraged. • Other drug combinations should be considered and probably are beneficial in proportion to the extent of BP reduction. However, combinations that have been successfully used in trials may be preferable. • Combinations of two antihypertensive drugs at fixed doses in a single tablet may be recommended and favored, because reducing the number of daily pills improves adherence, which is low in patients with hypertension. <u>Treatment strategies in white-coat and masked hypertension</u> • In white-coat hypertensives without additional risk factors, therapeutic intervention may be limited to lifestyle changes only, but this decision should be accompanied by close follow-up. • In white-coat hypertensives with a higher CV risk because of metabolic derangements or asymptomatic organ damage, drug treatment may be considered in addition to lifestyle changes. • In masked hypertension, both lifestyle measures and antihypertensive drug treatment should be considered, because this type of hypertension has been consistently found to have a CV risk very close to that of in- and out-of-office hypertension. <u>Antihypertensive treatment strategies in the elderly</u> • In elderly hypertensives with SBP ≥160 mmHg there is solid evidence to recommend reducing SBP to between 150 and 140 mmHg. • In fit elderly patients <80 years old antihypertensive treatment may be considered at SBP values ≥140 mmHg with a target SBP <140 mmHg if treatment is well tolerated. • In individuals older than 80 years with an initial SBP ≥160 mmHg, it is recommended to reduce SBP to between 150 and 140 mmHg, provided they are in good physical and mental conditions. • In frail elderly patients, it is recommended to leave decisions on antihypertensive therapy to the treating physician, and based on monitoring of the clinical effects of treatment. • Continuation of well-tolerated antihypertensive treatment should be considered when a treated individual becomes an octogenarian. • All hypertensive agents are recommended and can be used in the elderly, although diuretics and calcium antagonists may be preferred in isolated systolic hypertension. <u>Treatment strategies in hypertensive women</u> • Hormone therapy and selective estrogen receptor modulators are not recommended and should not be used for primary or secondary prevention of CVD.

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	• If treatment of younger perimenopausal women is considered for severe menopausal symptoms, the benefits should be weighed against potential risks. • Drug treatment of severe hypertension in pregnancy (SBP >160 mmHg or DBP >110 mmHg) is recommended. • Drug treatment may also be considered in pregnant women with persistent elevation of BP ≥150/95 mmHg, and in those with BP ≥140/90 mmHg in the presence of gestational hypertension, subclinical organ damage or symptoms. • In women at high risk of pre-eclampsia, provided they are at low risk of gastrointestinal hemorrhage, treatment with low dose aspirin from 12 weeks until delivery may be considered. • In women with child-bearing potential RAS blockers are not recommended and should be avoided. • Methyldopa, labetalol, and nifedipine should be considered preferential antihypertensive drugs in pregnancy. Intravenous labetalol or infusion of nitroprusside should be considered in case of emergency (pre-eclampsia). <u>Treatment strategies in patients with diabetes</u> • While initiation of antihypertensive drug treatment in diabetic patients whose SBP is ≥160 mmHg is mandatory, it is strongly recommended to start drug treatment also when SBP is ≥140 mmHg. • A SBP goal <140 mmHg is recommended in patients with diabetes. • The DBP target in patients with diabetes is recommended to be <85 mmHg. • All classes of antihypertensive agents are recommended and can be used in patients with diabetes; RAS blockers may be preferred, especially in the presence of proteinuria or microalbuminuria. • It is recommended that individual drug choice takes comorbidities into account. • Simultaneous administration of two blockers of the RAS is not recommended and should be avoided in patients with diabetes <u>Treatment strategies in hypertensive patients with metabolic syndrome</u> • Lifestyle changes, particularly weight loss and physical exercise, are to be recommended to all individuals with the metabolic syndrome. These interventions improve not only BP, but the metabolic components of the syndrome and delay diabetes onset. • As the metabolic syndrome can be considered a 'pre-diabetic' state, antihypertensive agents potentially improving or at least not worsening insulin sensitivity, such as RAS blockers and calcium antagonists, should be considered as the preferred drugs. Beta-blockers (with the exception of vasodilating β-blockers) and diuretics should be considered only as additional drugs, preferably in association with a potassium-sparing agent. • It is recommended to prescribe antihypertensive drugs with particular care in hypertensive patients with metabolic disturbances when BP is ≥140/90 mmHg after a suitable period of lifestyle changes, and to maintain BP <140/90 mmHg. • BP lowering drugs are not recommended in individuals with metabolic syndrome and high normal BP. <u>Therapeutic strategies in hypertensive patients with nephropathy</u> • Lowering SBP to <140 mmHg should be considered. • When overt proteinuria is present, SBP values <130 mmHg may be considered, provided that changes in eGFR are monitored. • RAS blockers are more effective in reducing albuminuria than other antihypertensive agents, and are indicated in hypertensive patients in the presence of microalbuminuria or overt proteinuria. • Reaching BP goals usually requires combination therapy, and it is recommended to combine RAS blockers with other antihypertensive agents.

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	• Combination of two RAS blockers, though potentially more effective in reducing proteinuria, is not recommended. • Aldosterone antagonists cannot be recommended in chronic kidney disease (CKD), especially in combination with a RAS blocker, because of the risk of excessive reduction in renal function and of hyperkalemia. <u>Therapeutic strategies in hypertensive patients with cerebrovascular disease</u> • It is not recommended to intervene with BP-lowering therapy during the first week after acute stroke irrespective of BP level, although clinical judgement should be used in the face of very high SBP values. • Antihypertensive treatment is recommended in hypertensive patients with a history of stroke or transient ischemic attack (TIA), even when initial SBP is in the 140 to 159 mmHg range. • In hypertensive patients with a history of stroke or TIA, a SBP goal of <140 mmHg should be considered. • In elderly hypertensives with previous stroke or TIA, SBP values for intervention and goal may be considered to be somewhat higher. • All drug regimens are recommended for stroke prevention, provided that BP is effectively reduced. <u>Therapeutic strategies in hypertensive patients with heart disease</u> • In hypertensive patients with CHD, a SBP goal <140 mmHg should be considered. • In hypertensive patients with a recent myocardial infarction, β-blockers are recommended. In case of other CHD all antihypertensive agents can be used, but β-blockers and calcium antagonists are to be preferred for symptomatic reasons (angina). • Diuretics, β-blockers, ACE inhibitors, angiotensin receptor blockers, and/or mineralocorticoid receptor antagonists are recommended in patients with heart failure or severe left ventricular (LV) dysfunction to reduce mortality and hospitalization. • In patients with heart failure and preserved ejection fraction (EF), there is no evidence that antihypertensive therapy per se or any particular drug is beneficial. However, in these patients, as well as in patients with hypertension and systolic dysfunction, lowering SBP to around 140 mmHg should be considered. Treatment guided by relief of symptoms (congestion with diuretics, high heart rate with β-blockers, etc.) should also be considered. • ACE inhibitors and angiotensin receptor blockers (and β-blockers and mineralocorticoid receptor antagonists if heart failure coexists) should be considered as antihypertensive agents in patients at risk of new or recurrent atrial fibrillation. • It is recommended that all patients with left ventricular hypertrophy (LVH) receive antihypertensive agents. • In patients with LVH, initiation of treatment with one of the agents that have shown a greater ability to regress LVH should be considered, i.e. ACE inhibitors, angiotensin receptor blockers, and calcium antagonists. <u>Therapeutic strategies in hypertensive patients with atherosclerosis, arteriosclerosis, and peripheral artery disease (PAD)</u> • In the presence of carotid atherosclerosis, prescription of calcium antagonists and ACE inhibitors should be considered as these agents have shown a greater efficacy in delaying atherosclerosis progression than diuretics and β-blockers. • In hypertensive patients with a pulse wave velocity above 10 m/s, all antihypertensive drugs should be considered provided that a BP reduction to <140/90 mmHg is consistently achieved. • Antihypertensive therapy is recommended in hypertensive patients with PAD to

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	achieve a goal of <140/90 mmHg, because of their high risk of myocardial infarction, stroke, heart failure, and CV death. • Though a careful follow up is necessary, β-blockers may be considered for the treatment of arterial hypertension in patients with PAD, since their use does not appear to be associated with exacerbation of PAD symptoms.

National Institute for Health and Clinical Excellence: **Hypertension in adults: diagnosis and management (2011)**[46]
 	
Reaffirmed Nov 2016
	Choosing antihypertensive drug treatment
	• 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 people ≥80 years of age the same antihypertensive drug treatment as people aged 55 to 80 years, taking into account any comorbidities.
	• Offer antihypertensive drug treatment to women of child-bearing potential in line with the recommendations on Management of pregnancy with chronic hypertension and Breastfeeding in 'Hypertension in pregnancy' (NICE clinical guideline 107).
	
	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). 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 step one antihypertensive (ACE inhibitor, ARB) with a calcium channel blocker (CCB) to patients >55 years of age and to black patients of African or Caribbean family origin 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 chlorthalidone (12.5 to 25.0 mg once daily) or indapamide (1.5 mg modified-release once daily or 2.5 mg once daily) in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide.
	• For patients who are already receiving treatment with bendroflumethiazide or hydrochlorothiazide and whose blood pressure is stable and well controlled, continue treatment as is.
	• β-blockers are not a preferred initial therapy for hypertension; however, β-blockers may be considered in younger patients, particularly:
	  ○ Patients with an intolerance or contraindication to ACE inhibitors and ARBs.
	  ○ Women of child-bearing potential.
	  ○ People with evidence of increased sympathetic drive.
	• If treatment is initiated with a β-blocker and a second antihypertensive is required, add a CCB over a thiazide-like diuretic to reduce the risk of developing diabetes.
	
	Step two treatment
	• If blood pressure is not controlled with a step one antihypertensive, offer a step two treatment with a CCB in combination with an ACE inhibitor or an ARB.
	• If a CCB is not appropriate or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic.
	• For black patients of African or Caribbean family origin, consider an ARB in preference to an ACE inhibitor, in combination with a CCB.
	
	Step three treatment
	• Before considering step three treatment, review medication to ensure step two treatment is at optimal or best tolerated doses.
	• If three drugs are required to control blood pressure, the combination of an ACE

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	inhibitor or ARB, CCB, and thiazide-like diuretic should be utilized.
	
	Step four treatment
	• Regard clinic blood pressure that remains >140/90 mmHg after treatment with the optimal or best tolerated doses of an ACE inhibitor or an ARB plus a CCB plus a diuretic as resistant hypertension, and consider adding a fourth antihypertensive drug and/or seeking expert advice.
	• For treatment of resistant hypertension at step four:
	  ○ Consider further diuretic therapy with low-dose spironolactone (25 mg once daily) if the blood potassium level is 4.5 mmol/l or lower. Use particular caution in people with a reduced estimated glomerular filtration rate because they have an increased risk of hyperkalemia.
	  ○ Consider higher-dose thiazide-like diuretic treatment if the blood potassium level is higher than 4.5 mmol/l.
	  ○ If further diuretic therapy for resistant hypertension is not tolerated or is contraindicated or ineffective, consider an α-blocker or β-blocker.

International Society on Hypertension in Blacks: **Management of High Blood Pressure in Blacks (2010)**[47]	• 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 (2012)**[48]	Blood pressure management in chronic kidney disease (CKD) non-dialysis (ND) patients without diabetes mellitus • The Work Group recommends that non-diabetic adults with CKD ND and urine albumin excretion <30 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >140 mm Hg systolic or >90 mm Hg diastolic be treated with blood pressure -lowering drugs to maintain a blood pressure that is consistently ≤140 mm Hg systolic and ≤90 mm Hg diastolic. • The Work Group suggests that non-diabetic adults with CKD ND and urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with BP-lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic. • The Work Group suggests that non-diabetic adults with CKD ND and urine albumin excretion >300 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with blood pressure -lowering drugs to maintain a blood pressure that is

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	consistently ≤130 mm Hg systolic and ≤ 80 mm Hg diastolic. • The Work Group suggests that an angiotensin receptor blocker (ARB) or angiotensin converting enzyme inhibitor (ACE-I) be used in non-diabetic adults with CKD ND and urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*) in whom treatment with blood pressure -lowering drugs is indicated. • The Work Group recommends that an ARB or ACE-I be used in non-diabetic adults with CKD ND and urine albumin excretion >300 mg per 24 hours (or equivalent*) in whom treatment with blood pressure -lowering drugs is indicated. <u>Blood pressure management in CKD ND patients with diabetes mellitus</u> • The Work Group recommends that adults with diabetes and CKD ND with urine albumin excretion <30 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >140 mm Hg systolic or >90 mm Hg diastolic be treated with BP-lowering drugs to maintain a blood pressure that is consistently ≤140 mm Hg systolic and ≤90 mm Hg diastolic. • The Work Group suggests that adults with diabetes and CKD ND with urine albumin excretion >30 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with BP-lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic. • The Work Group suggests that an ARB or ACE-I be used in adults with diabetes and CKD ND with urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*). • The Work Group recommends that an ARB or ACE-I be used in adults with diabetes and CKD ND with urine albumin excretion >300 mg per 24 hours (or equivalent*). <u>Blood pressure management in kidney transplant recipients (non–dialysis-dependent CKD of any stage with a kidney transplant [CKD T])</u> • The Work Group suggests that adult kidney transplant recipients whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic, irrespective of the level of urine albumin excretion. • In adult kidney transplant recipients, choose a blood pressure -lowering agent after taking into account the time after transplantation, use of calcineurin inhibitors, presence or absence of persistent albuminuria, and other co morbid conditions. <u>Blood pressure management in children with CKD ND</u> • The Work Group recommends that in children with CKD ND, blood pressure -lowering treatment is started when blood pressure is consistently above the 90th percentile for age, sex, and height. • The Work Group suggests that in children with CKD ND (particularly those with proteinuria), blood pressure is lowered to consistently achieve systolic and diastolic readings less than or equal to the 50th percentile for age, sex, and height, unless achieving these targets is limited by signs or symptoms of hypotension. • The Work Group suggests that an ARB or ACE-I be used in children with CKD ND in whom treatment with blood pressure -lowering drugs is indicated, irrespective of the level of proteinuria. <u>Blood pressure management in elderly persons with CKD ND</u> • Tailor blood pressure treatment regimens in elderly patients with CKD ND by carefully considering age, co-morbidities and other therapies, with gradual escalation of treatment and close attention to adverse events related to blood pressure treatment, including electrolyte disorders, acute deterioration in kidney function, orthostatic hypotension and drug side effects.

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	*Approximate equivalents for albumin excretion rate per 24 hours is expressed as protein excretion rate per 24 hours, albumin/creatinine ratio, protein/creatinine ratio, and protein reagent strip results.
American Diabetes Association: **Standards of Medical Care in Diabetes (2017)**[49]	Hypertension/blood pressure control • Blood pressure should be measured at every routine visit. Patients found to have elevated blood pressure should have blood pressure confirmed on a separate day. • Most patients with diabetes and hypertension should be treated to a systolic blood pressure goal of <140 mmHg and a diastolic blood pressure goal of <90 mmHg. • Lower systolic and diastolic blood pressure targets, such as 130/80 mmHg, may be appropriate for individuals at high risk of cardiovascular disease, if they can be achieved without undue treatment burden. • In pregnant patients with diabetes and chronic hypertension, blood pressure targets of 120 to 160/80 to 105 mmHg are suggested in the interest of optimizing long-term maternal health and minimizing impaired fetal growth. • Patients with confirmed office-based blood pressure >140/90 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). 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. • For patients with blood pressure >120/80 mmHg, lifestyle intervention consists of weight loss if overweight or obese; a Dietary Approaches to Stop Hypertension–style dietary pattern including reducing sodium and increasing potassium intake; moderation of alcohol intake; and increased physical activity. Coronary heart disease • In asymptomatic patients, routine screening for coronary artery disease is not recommended as it does not improve outcomes as long as atherosclerotic cardiovascular disease risk factors are treated. • Consider investigations for coronary artery disease in the presence of any of the following: atypical cardiac symptoms (e.g., unexplained dyspnea, chest discomfort); signs or symptoms of associated vascular disease including carotid bruits, transient ischemic attack, stroke, claudication, or peripheral arterial disease; or electrocardiogram abnormalities (e.g., Q waves). • In patients with known atherosclerotic cardiovascular disease, use aspirin and statin therapy (if not contraindicated) and consider ACE inhibitor therapy to reduce the risk of cardiovascular events. • In patients with prior myocardial infarction, β-blockers should be continued for at least two years after the event.

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	• In patients with symptomatic heart failure, thiazolidinedione treatment should not be used. • In patients with type 2 diabetes with stable congestive heart failure, metformin may be used if estimated glomerular filtration remains >30 mL/min but should be avoided in unstable or hospitalized patients with congestive heart failure. Diabetic 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, in all patients with type 2 diabetes, and in all patients with comorbid hypertension. • Optimize glucose control to reduce the risk or slow the progression of diabetic kidney disease. • Optimize blood pressure control to reduce the risk or slow the progression of diabetic kidney disease. • For people with nondialysis-dependent diabetic kidney disease, dietary protein intake should be approximately 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. • 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) B 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 or changes in potassium when ACE inhibitors, angiotensin receptor blockers, or diuretics are used. • Continued monitoring of urinary albumin–to–creatinine ratio in patients with albuminuria treated with an ACE inhibitor or an angiotensin receptor blocker is reasonable to assess the response to treatment and progression of diabetic kidney disease. • An ACE inhibitor or an angiotensin receptor blocker is not recommended for the primary prevention of diabetic kidney disease 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. • When estimated glomerular filtration rate is <60 mL/min/1.73 m^2, evaluate and manage potential complications of chronic kidney disease. • Patients should be referred for evaluation for renal replacement treatment if they have an estimated glomerular filtration rate <30 mL/min/1.73 m^2. • Promptly refer to a physician experienced in the care of kidney disease for uncertainty about the etiology of kidney disease, difficult management issues, and rapidly progressing kidney disease.
American Academy of Family Physicians: **Treatment of Acute Migraine Headache (2011)**[50]	General treatment principles • Because relatively few trials have directly compared the different medication classes available to treat acute migraine, definitive treatment algorithms cannot be developed. • Nonsteroidal anti-inflammatory drugs (NSAIDs) or caffeine-containing combination analgesics may be first-line treatment for mild to moderate migraine, or severe migraine that has previously responded to these agents. • Triptans are considered first-line abortive treatment of moderate to severe migraine, or mild attacks that have not responded to nonprescription medicines. Ergotamine-containing compounds may also be reasonable in this situation.
American Academy of Family Physicians: **Medications for**	• First-line therapies for migraine prophylaxis in adults include propranolol, timolol, amitriptyline, divalproex, sodium valproate, and topiramate. • Second-line therapies for migraine prophylaxis in adults (listed by evidence of

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Migraine Prophylaxis (2006)[51]	effectiveness) include gabapentin, naproxen, naproxen sodium, timed-release dihydroergotamine mesylate, candesartan, lisinopril, atenolol, metoprolol, nadolol, fluoxetine, verapamil, magnesium, vitamin B2, coenzyme Q10, hormone therapy, feverfew, and botulinum toxin type A injections.
American Academy of Neurology/ American Headache Society: **Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults (2012)[52]**	• The following medications are established as effective and should be offered for migraine prevention: ○ Antiepileptic drugs (AEDs): divalproex sodium, sodium valproate, topiramate ○ 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
European Federation of Neurological Societies: **Guideline on the Drug Treatment of Migraine - Revised Report of an European Federation of Neurological Societies Task Force (2009)[53]**	• Prophylactic drugs for the treatment of migraine with good efficacy and tolerability and evidence of efficacy are β-blockers, calcium-channel blockers, antiepileptic drugs, NSAIDs, antidepressants, and miscellaneous drugs. • The use of all these drugs is based on empirical data rather than on proven pathophysiological concepts. • There is no commonly accepted indication for starting a prophylactic treatment. Prophylactic drug treatment of migraine should be considered and discussed with the patient when 1) the quality of life, business duties, or school attendance are severely impaired; 2) frequency of attacks per month is two or higher; 3) migraine attacks do not respond to acute drug treatment; or 4) frequent, very long, or uncomfortable auras occur. • The recommended drugs of first choice are β-blockers (metoprolol or propranolol), calcium-channel blockers (flunarizine), and antiepileptic drugs (valproic acid or topiramate). • Drugs of second choice include amitriptyline, venlafaxine, naproxen, and bisoprolol. • Drugs of third choice include acetylsalicylic acid, gabapentin, magnesium, riboflavin, coenzyme Q10, candesartan, lisinopril, and methylsergide. • β-blockers are clearly effective in migraine prophylaxis and very well studied. The best evidence has been obtained for metoprolol and propranolol. Bisoprolol, timolol and atenolol might be effective, but evidence is less convincing compared with propranolol and metoprolol. • The calcium-channel blocker, flunarizine, has been shown to be effective in migraine prophylaxis in several studies. • Valproic acid and topiramate are two antiepileptic drugs with evidence of efficacy in more than one placebo-controlled trial. The efficacy rates are comparable to those of metoprolol, propranolol, and flunarizine. Topiramate is also efficacious in the prophylaxis of chronic migraine and may have some effect in migraine with medication overuse.
National Cancer Institute: **Pheochromocytoma and Paraganglioma Treatment (PDQ®) (2015)[54]**	• 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. • 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

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	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-blocker 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.
American Academy of Neurology: **Practice Parameter: Therapies for Essential Tremor: Report of the Quality Standards Subcommittee of the American Academy of Neurology (2005)[55], Evidence-based guideline update: Treatment of essential tremor (2011 update)[56]** **Reaffirmed April 2014**	• 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 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

*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							✔ (succinate)		
Hypertension									
Control of blood pressure in severe hypertension						✔ (injection)			
Essential hypertension					✔ ‡				
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	Propranolol and HCTZ
Angina Pectoris										
Angina pectoris			✔ * (Inderal LA®, tablet)							
Cardiac Arrhythmias										

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	Propranolol and HCTZ
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				✔ † (Betapace®, Sotylize®)						
Maintenance of normal sinus rhythm in patients with symptomatic atrial fibrillation/atrial flutter who are currently in sinus rhythm				✔ † (Betapace AF®, Sotylize®)						
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 hypertropic 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			✔ (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	Propranolol and HCTZ
control blood pressure and reduce symptoms of catecholamine-secreting tumors										
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® 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.[32,34]

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	<5	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)	12 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)	6 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)	17 to 26	High
Pindolol	87 to 90	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 4	High
Sotalol	90 to 100	0	Liver, minor	Renal (66 to 88)	7 to 18	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	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Propranolol and HCTZ	Not reported	Not reported	Not reported	Not reported	Not reported	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 or IC Antiarrhythmic Agents	Class IA and IC 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.

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[1-22]

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	1 to 10	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	-	1 to 10	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	1 to 10	1 to 10	<2	<1	9 to 20	1 to 5	1 to 27	-	-
Myocardial ischemia	-	-	-	-	-	-	-	-	<1
Orthostatic hypotension	-	-	-	<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	-	-	-	-	-	-
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	-	-	-	-	-	-	-	>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[1-22]

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	Propranolol and HCTZ
Cardiovascular										
Angina	-	-	✔	-	✔	-	-	-	-	✔
Arrhythmia	1 to 10	-	-	5	✔	-	<1	-	<1	-
Arterial/vascular insufficiency	-	-	✔	-	-	-	-	1	-	✔
Atrioventricular nodal disturbances	-	-	✔	-	-	-	-	-	-	✔
Bradycardia	<1	≤2	6	13 to 16	1 to 10	1 to 10	<1	2 to 16	1 to 10	6
Cardiac failure/arrest	-	-	-	-	✔	-	-	-	-	-
Cardiogenic shock	-	-	✔	-	-	-	-	✔	-	✔
Chest pain	-	3	2 to 4	3 to 16	-	1 to 10	1 to 2	1	<1	2 to 4
Cold extremities	<1	≤2	✔	<1	✔	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	6	2	8	✔	1 to 10	<1	-	1 to 10	2
Electrocardiogram abnormal	-	-	-	7	-	-	-	-	-	-
Flushing	-	-	-	-	-	-	<1	-	-	-
Heart block	<1	≤2	-	-	✔	1 to 10	-	5	-	-
Hypotension	<1	≤2	✔	6	✔	1 to 10	1 to 10	1 to 27	-	1 to 10
Myocardial contractility impaired	-	-	✔	-	-	-	<1	<1	-	<1
Myocardial ischemia	-	-	-	-	-	-	-	-	-	-
Orthostatic hypotension	-	-	-	-	-	-	1 to 10	1 to 10	<1	1 to 10
Palpitations	-	≤1	-	14	✔	-	<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	-	-	-	-	-	-	3
Amnesia	-	-	✔	-	-	-	-	-	-	✔
Anxiety	-	-	-	4	✔	-	<1	✔	-	-
Catatonia	-	-	✔	-	-	-	-	-	-	✔
Cerebral ischemia	-	-	-	-	✔	-	-	-	-	-
Cerebral vascular accident	-	-	-	-	✔	-	-	-	-	-
Cognitive dysfunction	-	-	✔	-	-	-	-	-	-	✔
Confusion	<1	-	✔	6	✔	1 to 10	<1	✔	<1	✔
Depression	1 to 10	-	1 to 3	4	✔	1 to 10	<1	5	1 to 10	1 to 3
Disorientation	-	-	-	-	✔	-	-	-	✔	-
Dizziness	1 to 10	9	2 to 11	20	1 to 10	1 to 10	<1	2 to 10	-	2 to 11
Drowsiness	-	-	2	-	-	-	-	-	>10	2

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	Propranolol and HCTZ
Emotional lability	-	-	✔	<1	-	-	-	-	-	✔
Fatigue	1 to 10	8	3 to 17	20	1 to 10	1 to 10	6 to 8	1 to 10	✔	3 to 17
Hallucinations	-	<1	✔	-	✔	<1	<1	✔	<1	✔
Headache	1 to 10	-	1 to 9	8	-	1 to 10	<1	✔	<1	1 to 9
Hyper/hypoesthesia	-	-	-	-	-	-	1 to 2	-	-	-
Insomnia	<1	10	3 to 8	-	✔	1 to 10	2 to 3	✔	>10	3 to 8
Lethargy	<1	-	4	-	-	1 to 10	-	-	-	4
Lightheadedness	-	-	✔	12	-	-	-	-	-	✔
Malaise	-	-	-	-	-	-	<1	-	-	-
Memory loss	-	-	-	-	✔	-	<1	✔	-	-
Mental impairment	-	-	-	-	-	1 to 10	-	-	-	-
Nervousness	-	7	2	-	✔	-	<1	✔	<1	2
Nightmares/vivid dreams	<1	5	✔	-	✔	1 to 10	-	✔	✔	✔
Paresthesia	-	-	-	-	-	<1	<1	✔	-	-
Psychosis	-	-	✔	-	-	<1	-	-	-	✔
Sleep disturbance	-	-	-	8	-	-	<1	✔	-	-
Somnolence	-	-	✔	-	✔	-	<1	✔	✔	✔
Vertigo	-	-	✔	<1	-	-	<1	✔	-	✔
Dermatologic										
Acne	-	-	-	-	-	-	<1	-	-	-
Alopecia	-	-	✔	<1	✔	<1	<1	<1	-	<1
Cutaneous ulcers	-	-	✔	-	-	-	-	-	-	✔
Dermatitis	-	-	✔	-	-	-	-	-	-	✔
Eczematous eruptions	-	-	✔	-	-	-	-	-	-	✔
Erythema multiforme	-	-	✔	-	-	-	<1	<1	✔	<1
Exfoliative dermatitis	-	-	✔	-	-	-	<1	<1	✔	<1
Hyperkeratosis	-	-	✔	-	-	-	-	-	-	✔
Nail changes	-	-	✔	-	-	-	-	-	-	✔
Oculomucocutaneous reactions	-	-	✔	-	-	-	-	-	-	✔
Photosensitivity	-	-	-	<1	-	1 to 10	1 to 10	1 to 10	✔	1 to 10
Pruritus	-	1	✔	<1	-	-	<1	5	-	✔
Pseudo pemphigoid	-	-	-	-	✔	-	-	-	-	-
Psoriasiform rash	-	-	✔	-	✔	<1	<1	-	-	✔
Psoriasis (exacerbated)	-	-	-	-	✔	-	<1	✔	✔	-
Purpura	-	-	-	-	-	<1	<1	-	✔	-
Rash	-	-	0 to 2	5	✔	<1	<1	5	-	0 to 2
Red crusted skin	-	-	-	<1	-	-	-	-	-	-
Skin necrosis after extravasation	-	-	-	<1	-	-	-	-	-	-
Stevens-Johnson syndrome	-	-	✔	-	-	-	<1	<1	-	<1
Sweating, excessive	-	≤2	2	<1	-	-	-	✔	-	2
Toxic epidermal necrolysis	-	-	✔	-	-	-	<1	<1	✔	<1
Ulcers	-	-	✔	-	-	-	-	-	-	✔
Urticaria	-	-	✔	5	✔	<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	Propranolol and HCTZ
Diabetes (exacerbated)	-	-	-	-	-	-	-	✔	✔	-
Glycosuria	-	-	-	-	-	<1	-	-	-	-
Gout	-	-	-	-	-	<1	<1	-	-	-
Hypoglycemia masked	-	-	-	-	✔	-	-	-	-	-
Libido decreased	-	-	-	-	✔	-	-	✔	-	-
Gastrointestinal										
Abdominal pain	-	-	1	-	-		<1	✔	-	1
Anorexia	-	-	✔	-	✔	1 to 10	1 to 10	1 to 10	✔	1 to 10
Constipation	-	-	0 to 2	-	-	1 to 10	<1	1	1 to 10	0 to 2
Cramping	-	-	✔	-	-				✔	✔
Diarrhea	1 to 10	≤2	2 to 7	7	✔	1 to 10	3 to 4	5	1 to 10	2 to 7
Dry mouth	-	-	-	-	✔				-	-
Dyspepsia	1 to 10	-	1 to 7	-	✔		<1		✔	1 to 7
Epigastric distress	-	-	-	-	-	1 to 10	1 to 10	1 to 10	-	1 to 10
Flatulence	-	-	4	2	-			1	-	4
Gastritis/gastric irritation	-	-	-	-	-	-	<1			
Heartburn	-	-	-	-	-	-	-	1	-	-
Ischemic colitis	<1	-	✔	-	-				-	✔
Melena	-	-	-	-	-				✔	-
Nausea	1 to 10	5	1 to 6	10	✔	1 to 10	2	1	1 to 10	1 to 6
Pancreatitis	-	-	-	-	-	<1		<1	-	<1
Peptic ulcer	-	-	-	-	-	-	<1			
Periodontitis	-	-	-	-	-				✔	-
Retroperitoneal fibrosis	-	-	-	-	✔			✔	-	-
Stomach discomfort	-	-	✔	3 to 6	-				1 to 10	✔
Taste disorder	-	-	-	-	-		<1	✔	✔	-
Vomiting	-	≤2	✔	10	-	<1	1 to 2	✔	1 to 10	✔
Weight gain	-	≤2	-	-	-		<1	✔	-	-
Xerostomia	-	-	-	-	-	-	<1	-	-	-
Genitourinary										
Cystitis	-	-	-	-	-	-	<1	-	-	-
Impotence	-	≤2	1	2	✔	1 to 10	<1	✔	-	1
Interstitial nephritis	-	-	✔	-	-	-	-	-	-	✔
Micturition (frequency)	-	-	1	-	-	-	-	-	-	1
Oliguria	-	-	✔	-	-	-	-	-	-	✔
Polyuria	-	≤2	-	-	-	<1	<1	-	-	-
Proteinuria	-	-	✔	-	-	-	-	-	-	✔
Sexual ability decreased	-	-	-	3	-	-	<1	-	>10	-
Hematologic										
Agranulocytosis	-	-	✔	-	-	<1	-	<1	-	<1
Anemia (aplastic/hemolytic)	-	-	-	-	-	<1	-	<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	Propranolol and HCTZ
Leukopenia	-	-	-	<1	-	<1	<1	<1	<1	<1
Prothrombin decreased	-	-	-	-	-	-	-	-	✔	-
Purpura	<1	-	✔	-	-	<1	-	-	-	✔
Thrombocytopenia	<1	-	✔	<1	-	<1	<1	<1	<1	✔
Hepatic										
Cholestatic jaundice	-	-	-	-	-	-	-	-	✔	-
Hepatic impairment	-	-	-	-	-	<1	-	<1	-	<1
Hepatitis	-	-	-	-	-	-	-	✔	-	-
Increase liver enzymes	-	7	-	-	-	<1	-	-	-	-
Transaminases increase	-	-	✔	<1	-	-	<1	✔	-	✔
Laboratory Test Abnormalities										
Alkaline phosphatase increased	-	<1	✔	-	-	-	-	✔	-	✔
Electrolyte imbalance	-	-	-	-	-	-	-	-	✔	-
Hypercalcemia	-	-	-	-	-	<1	-	<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	-	1 to 10
Hyponatremia	-	-	-	-	-	<1	-	-	-	-
Lactate dehydrogenase increased	-	<1	-	-	-	-	-	✔	-	-
Musculoskeletal										
Arthralgia	1 to 10	7	1	-	-	-	1 to 10	✔	-	1
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	-	-	-	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	Propranolol and HCTZ
Restlessness	-	-	-	-	-	<1	<1	-	-	--
Tremor	-	-	-	-	-	-	<1	-	✔	-
Twitching	-	-	-	-	-	-	<1	-	-	-
Weakness	-	4	1	13	-	<1	-	-	✔	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	-	-	-	2	-	-	<1	-	-	-
Bronchitis	-	-	-	-	-	-	<1	-	-	-
Bronchospasm	<1	-	✔	-	✔	-	<1	1	1 to 10	✔
Cough	<1	-	1	-	✔	-	<1	-	-	1
Dyspnea	-	5	1 to 6	21	1 to 10	<1	1 to 2	1 to 3	<1	1 to 6
Eosinophilic pneumonitis	-	-	-	-	-	-	-	<1	-	<1
Laryngospasm	-	-	✔	-	-	-	-	-	-	✔
Nasal congestion	-	-	-	-	✔	-	-	-	-	-
Nasopharyngitis	-	-	-	-	-	-	-	-	✔	-
Pharyngitis	-	-	✔	-	-	-	<1	-	-	✔
Pulmonary edema	-	-	✔	<1	✔	-	-	-	-	✔
Respiratory failure	-	-	✔	-	✔	-	-	<1	-	<1
Rhinitis	-	-	1	-	-	-	3 to 4	✔	-	1
Sinusitis	-	-	-	-	-	-	2	-	-	-
Upper respiratory infection	-	-	5	5 to 8	-	-	5	-	-	5
Wheezing	-	≤2	✔	-	-	<1	-	1	✔	✔
Special Senses										
Abnormal/blurred vision	-	-	3	-	-	-	-	✔	-	3
Burning	-	≤2	-	-	-	-	-	-	-	-
Corneal sensitivity decrease	-	-	-	-	✔	-	-	-	-	-
Cystoid macular edema	-	-	-	-	✔	-	-	-	-	-
Diplopia	-	-	-	-	✔	-	-	-	-	-
Dry eyes	-	-	-	-	✔	-	-	✔	-	-
Eye discomfort/pain	-	≤2	-	-	-	-	<1	-	-	-
Hearing decreased	-	-	-	-	-	-	<1	-	-	-
Hyperemia of conjunctiva	-	-	✔	-	-	-	-	-	-	✔
Keratitis	-	-	-	-	✔	-	-	-	-	-
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**	**Propranolol and HCTZ**
Refractive changes	-	-	-	-	✔	-	-	-	-	-
Tinnitus	-	-	-	-	✔	-	<1	-	-	-
Visual disturbances	-	≤2	✔	5	✔	-	<1	✔	-	✔
Xerophthalmia	-	-	✔	-	-	-	-	-	-	✔
Other										
Allergy	-	-	-	-	✔	-	-	<1	-	<1
Anaphylactoid reaction	-	-	✔	-	-	-	-	-	-	✔
Angioedema	-	-	-	-	✔	-	-	-	✔	-
Cholecystitis	-	-	-	-	-	<1	-	-	-	-
Cutaneous vasculitis	-	-	-	-	-	<1	<1	-	-	-
Gangrene	-	-	-	-	-	-	-	✔	-	-
Hypervolemia	-	-	-	-	-	-	-	-	✔	-
Lupus syndrome	-	-	✔	-	✔	<1	-	-	✔	✔
Mesenteric arterial thrombosis	<1	-	-	-	-	-	-	-	-	-
Necrotizing angitis	-	-	-	-	-	<1	-	-	-	-
Peyronie's disease	-	-	✔	-	✔	<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[3-22]

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 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 tablet (NYHA Class II): initial, 25 mg/day; maintenance, double the dose every two weeks up to 200 mg/day or highest dose tolerated Extended-release tablet (NYHA Class >II): initial, 12.5 mg/day; maintenance, double the dose every two weeks up to 200 mg/day or highest dose tolerated Hypertension: Extended-release 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 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 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;	Safety and efficacy in children have not been	Tablet: 2.5 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	maintenance, increase in two week intervals until optimal response; maximum, 40 mg/day	established.	5 mg 10 mg 20 mg
Penbutolol	Hypertension: Tablet: initial, 20 mg once daily; maintenance, 20 mg once daily, usual dose 10 to 40 mg once daily; maximum, 80 mg/day	Safety and efficacy in children have not been established.	Tablet: 20 mg
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	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
	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®): 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	Injection: 5 mg/ mL Solution: 5 mg/mL Tablet: 80 mg 120 mg 160 mg 240 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		daily; neonate dosing available for Sotylize® Solution, tablet (Betapace®, Sotylize®; ventricular Arrhythmias): 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®	
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	Safety and efficacy in children have not been established.	Extended-release tablet: 25-12.5 mg 50-12.5 mg 100-12.5 mg Tablet: 50-25 mg 100-25 mg 100-50 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	administered in single or divided doses		
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: 40-5 mg 80-5 mg
Propranolol and HCTZ	Hypertension: Tablet: initial, 40-25 mg twice daily; maintenance, may gradually increase dose until desired response is achieved up to 160 to 480 mg/day; maximum, 160 mg of propranolol	Safety and efficacy in children have not been established.	Tablet: 40-25 mg 80-25 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.[57] (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.[58] (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.[59] (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.[60] (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.[61] (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.[62] (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.[63] (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.[64] (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 Weeks 7 to 10: 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.[65] (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.[66] (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.[67] (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.[68] (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.[69] (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.[70] (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.[71] (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.[72] (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.[73] (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.[74] (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.[75] (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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(-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[76] (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[77] (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.[78] (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.[79] (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.[80] (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.[81] (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.[82] (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.[83] (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;

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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.[84] (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.[85] (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.[86] (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.[87] (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.[88] (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.[89] (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.[90] (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.[91] (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.[92] (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.[93] (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.[94] (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.[95] (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[96] (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.[97] (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.[98] (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.[99] (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.[100] (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.[101] (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.[102] (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.[103] (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 Weeks 5 to study end: 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.[104] (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.[105] (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.[106] (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.[107] (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.[108] (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.[109] (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.[110] (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.[111] (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.[112] (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.[113] (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.[114] (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.[115] (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.[116] (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.[117] (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.[118]	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.[119] (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.[120] (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.[121] (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.[122] (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.[123] (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.[124] (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.[125] (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.[126] (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.[127] (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.[128] (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.[129] (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.[130] (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.[131] (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.[132] (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.[133] (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.[134]	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.[135] (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.[136] (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.[137] (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.[138] (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.[139] (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.[140] (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[141] (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.[142] (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.[143]	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[144] (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.[145] (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.[146] (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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Casas et al.[147] (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.[148] (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.[149] (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.[150] (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.[151] (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.[152] (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.[153] (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.[154] (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.[155] (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.[156] (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.[157] (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.[158] (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.[159] (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.[160] (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.[161]	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) Conventional drug group Atenolol 50 mg QD, HCTZ 25 mg QD plus amiloride 2.5 mg QD, metoprolol 100 mg QD, or pindolol 5 mg QD vs Newer drug group 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.[162] (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.[163] (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.[164] (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.[165] (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.[166] (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.[167] (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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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.[168] (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.[169] (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.[170] (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.[171] (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[172] (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.[173] (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.[174] (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.[175] (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.[176] (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.[177] (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.[178] (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.[179] (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.[180] (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.[181] (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.[182] (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.[183] (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.[114]

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	$$$$	$
Atenolol	tablet	Tenormin®*	$$$$	$
Betaxolol	tablet	N/A	N/A	$
Bisoprolol	tablet	N/A	N/A	$
Carvedilol	extended-release capsule, tablet	Coreg®*, Coreg CR®	$$$$$	$
Labetalol	injection, tablet	N/A	N/A	$$$
Metoprolol	extended-release tablet, injection, tablet	Lopressor®*, Toprol-XL®*	$$$$$	$
Nadolol	tablet	Corgard®*	$$$$$	$$$$
Nebivolol	tablet	Bystolic®	$$$$$	N/A
Penbutolol	tablet	Levatol®	$$$$	N/A
Pindolol	tablet	N/A	N/A	$
Propranolol	extended-release capsule, injection,	Hemangeol®, Inderal LA®*, Inderal XL®, InnoPran XL®	$$$$$	$$

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

*Generic is available in at least one dosage form or strength.
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.[1-22] 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.[1-22] These agents differ with regards to their adrenergic-receptor blockade, membrane stabilizing and intrinsic sympathomimetic activities, as well as lipophilicity.[1,2,25] All of the agents are available in a generic formulation, with the exception of nebivolol and penbutolol.

Several national and international guidelines address the use of β-blockers.[26-56] 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, and post-myocardial infarction. [26-56] There are several published guidelines on the treatment of hypertension. Thiazide-type diuretics are frequently recommended as initial therapy in patients with uncomplicated hypertension.[42-48] 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).[42] Several guidelines consistently recommend that the selection of an antihypertensive agent be based on compelling indications for use.[42-48] Most patients will require more than one antihypertensive medication to achieve blood pressure goals.[42-47] β-blockers are recommended as one of several initial options for the prevention of migraine headaches (metoprolol and propranolol), as well as for the treatment of essential tremor (propranolol).[50-53,55,56] Although no uniform guidelines for the treatment of infantile hemangiomas are currently available, the oral solution formulation of propranolol, under the brand name Hemangeol®, is the first agent to gain FDA-approval for this indication.[12] Propranolol is considered the first-line agent for infantile hemangiomas requiring systemic treatment.[24]

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.[102-148] Most patients will require more than one antihypertensive agent to achieve blood pressure goals.[42-47] The use of a fixed-dose combination product may simplify the treatment regimen and improve adherence.[44,45] 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.[105]

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.[57-65] 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.[76-83,86,87,91-94,96-98] 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.[6]

In general, adverse events are similar among the β-blockers. Common adverse effects include fatigue, cold hands, dizziness, and weakness.[1-22] 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.[23,25]

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
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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.[3-5] 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.[1-5]

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.[1,2,6-17] 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. Since the last review, amlodipine has also been approved in a combination formulation with perindopril, under the brand name Prestalia®. 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 and amlodipine-perindopril are available in a generic formulation. This class was last reviewed in August 2015.

Table 1. Dihydropyridines Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Amlodipine	tablet	Norvasc®*	amlodipine
Clevidipine	injection^	Cleviprex®	none
Felodipine	extended-release tablet	N/A	felodipine
Isradipine	capsule	N/A	isradipine
Nicardipine	capsule*, injection	Cardene-Dex®^, Cardene-NACL®^	nicardipine
Nifedipine	capsule, extended-release tablet	Adalat CC®*, Procardia®*, 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®*	none
Amlodipine and perindopril	tablet	Prestalia®	none
Amlodipine and valsartan	tablet	Exforge®*	none

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Amlodipine, valsartan, and hydrochlorothiazide	tablet	Exforge HCT®*	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 dihydropyridines are summarized in Table 2.

Table 2. Treatment Guidelines Using the Dihydropyridines

Clinical Guideline	Recommendations
American College of Cardiology/American Heart Association: **2007 Chronic Angina Focused Update of the 2002 Guidelines for the Management of Patients With Chronic Stable Angina (2007)**[18]	• Aspirin should be started at 75 to 162 mg/day and continued indefinitely in all patients, unless contraindicated. • Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with an increased risk of bleeding and should be monitored closely. • Patients with hypertension and established coronary artery disease (CAD) should be treated with blood pressure medication(s) as tolerated, including angiotensin converting enzyme (ACE) inhibitors and/or β-adrenergic antagonists (β-blockers) with the addition of other medications as needed to achieve blood pressure goals of <140/90 or <130/80 mm Hg for patients with chronic kidney disease or diabetes. • Long-acting calcium channel blocking agents or long-acting nitrates may be used if β-blockers are contraindicated. Immediate-release and short-acting dihydropyridine calcium channel blockers can increase adverse cardiac events and should not be used. • Long-acting calcium channel blockers or long-acting nitrates may be used with β-blockers if initial treatment is not successful. • ACE inhibitors should be used indefinitely in patients with a left ventricular ejection fraction (LVEF) ≤40% and in those with hypertension, diabetes or chronic kidney disease, unless contraindicated. • ACE inhibitors should also be used indefinitely in patients at lower risk (mildly reduced or normal LVEF in whom cardiovascular risk factors remain well controlled and revascularization has been performed), unless contraindicated. • Angiotensin II receptor blockers (ARBs) are recommended in patients with hypertension, those who have an indication for an ACE inhibitor and are intolerant to them, who have heart failure, or who have had a myocardial infarction (MI) and have a LVEF ≤40%. • ARBs may be considered in combination with an ACE inhibitor for heart failure due to left ventricular systolic dysfunction. • Aldosterone blockade is recommended in patients post-MI without significant renal dysfunction or hyperkalemia who are already receiving therapeutic doses of an ACE inhibitor and a β-blocker, have a LVEF ≤40% and have either diabetes or heart failure. • It is beneficial to start and continue β-blocker therapy indefinitely in all patients who have had a MI, acute coronary syndrome or left ventricular dysfunction with or without heart failure symptoms, unless contraindicated. • Annual influenza vaccination is recommended in patients with cardiovascular disease.
European Society of Cardiology: **Guidelines on the Management of**	<u>General management of stable coronary artery disease (SCAD) patients</u> • The goal of management of SCAD is to reduce symptoms and improve prognosis. • The management of CAD patients encompasses lifestyle modification, control of CAD risk factors, evidence-based pharmacological therapy, and patient education.

Clinical Guideline	Recommendations
Stable Coronary Artery Disease (2013)[19]	<u>General considerations for pharmacological treatments in SCAD patients</u> • 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. <u>Pharmacological treatments for angina/ischemia relief in SCAD patients</u> • Short-acting nitrates are recommended. • First-line treatment is indicated with ß-blockers and/or calcium channel blockers to control heart rate and symptoms. • For second-line treatment it is recommended to add long-acting nitrates or ivabradine or nicorandil* or ranolazine, according to heart rate, blood pressure, and tolerance. • For second-line treatment, trimetazidine* may be considered. • 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 β-blockers avoided. <u>Pharmacological treatments for event prevention in SCAD patients</u> • Low-dose aspirin daily is recommended in all SCAD patients. • Clopidogrel is indicated as an alternative in case of aspirin intolerance. • Statins are recommended in all SCAD 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. • β-blockers are recommended as a first line treatment. • Calcium antagonists are recommended if β-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 (aminophylline, bamiphylline*) or non-pharmacological treatments such as neurostimulatory techniques may be considered in patients with symptoms refractory to the above listed drugs.
American College of Physicians/ American College of Cardiology Foundation/ American Heart Association/ American Association for Thoracic Surgery/ Preventive Cardiovascular Nurses Association/	<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

Clinical Guideline	Recommendations
Society of Thoracic Surgeons: **Management of Stable Ischemic Heart Disease (2012)[20]**	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 Management of Patients With Non–ST-Elevation Acute Coronary Syndromes (2014)[21]**	<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
	  ○ 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.

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	○ 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 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

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	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 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.

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	Late hospital care, hospital discharge, and posthospital discharge care
	• 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 patients treated with ticagrelor and 81 to 325 mg daily in all other patients.
	  ○ 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.
	  ○ 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
	  ○ 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.
	  ○ 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: **Guideline for the Management of Acute Coronary Syndromes in Patients Presenting Without Persistent ST-Segment Elevation (2015)**[22]	Pharmacological treatment of ischemia • Early initiation of β-blocker treatment is recommended in patients with ongoing ischemic symptoms and without contraindications. • 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. Recommendations for platelet inhibition in non-ST-elevation acute coronary syndromes

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	• 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.
	  ○ 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.
	• 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>

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	• In patients with a firm indication for oral anticoagulation (e.g., atrial fibrillation with a CHADS2-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. • 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 CHADS2-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.
American College of Cardiology/American Heart Association: **Guideline for the Management of ST-Elevation Myocardial Infarction (2013)**[23]	Routine medical therapies: calcium channel blockers • 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. Routine medical therapies: β-blockers • 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

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	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 (2012)**[24]	<u>Routine therapies in the acute, subacute and long term phase of STEMI</u> • Active smokers with STEMI must receive counseling and be referred to a smoking cessation program. • Each hospital participating in the care of STEMI patients must have a smoking cessation protocol. • Exercise-based rehabilitation is recommended. • Antiplatelet therapy with low dose aspirin (75 to 100 mg) is indicated indefinitely after STEMI. • In patients intolerant to aspirin, clopidogrel is indicated as an alternative. • Dual antiplatelet therapy with a combination of aspirin and prasugrel or aspirin and ticagrelor is recommended (over aspirin and clopidogrel) in patients treated with PCI. • Dual antiplatelet therapy with aspirin and an oral ADP receptor antagonist must be continued for up to 12 months after STEMI, with a strict minimum of 1 month for patients receiving bare metal stent and 6 months for patients receiving drug-eluting stent. • In patients with left ventricular thrombus, anticoagulation should be instituted for a minimum of 3 months. • In patients with a clear indication for oral anticoagulation (e.g. atrial fibrillation with CHA2DS2-VASc Score ≥2 or mechanical valve prosthesis), oral anticoagulation must be implemented in addition to antiplatelet therapy. • If patients require triple antithrombotic therapy, combining dual antiplatelet therapy and oral anticoagulant, e.g. because of stent placement and an obligatory indication for oral anticoagulation, the duration of dual antiplatelet therapy should be minimized to reduce bleeding risk. • 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 1 year in patients with STEMI who did not receive a stent. • Gastric protection with a proton pump inhibitor should be considered for the duration of DAPT therapy in patients at high risk of bleeding. • 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. • Intravenous β-blockers must be avoided in patients with hypotension or heart failure.

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	• Intravenous β-blockers should be considered at the time of presentation in patients 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. • Reassessment of LDL-cholesterol should be considered after 4–6 weeks to ensure that a target value of ≤70 mg/dL has been reached. • Verapamil may be considered for secondary prevention in patients with absolute contraindications to β-blockers and no heart failure. • 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.

National Institute for Health and Clinical Excellence: **Myocardial Infarction: cardiac rehabilitation and prevention of further cardiovascular disease (2013)**[25]	Drug therapy
	• Offer all people who have had an acute MI treatment with the following drugs:
	  ○ ACE inhibitor
	  ○ Dual antiplatelet therapy (aspirin plus a second antiplatelet agent)
	  ○ β-blocker
	  ○ Statin
	
	Antiplatelet therapy
	• Offer aspirin to all people after an MI and continue indefinitely, unless they are aspirin intolerant or have an indication for anticoagulation.
	• Offer aspirin to people who have had an MI more than 12 months ago and continue it indefinitely.
	• For patients with aspirin hypersensitivity, clopidogrel monotherapy should be considered as an alternative treatment.
	• Special considerations should be made for people with dyspepsia.
	• After appropriate treatment, people with a history of aspirin-induced ulcer bleeding whose ulcers have healed and who are negative for Helicobacter pylori should be considered for treatment in line with dyspepsia.
	• Ticagrelor in combination with low-dose aspirin is recommended for up to 12 months as a treatment option in adults with ACS (STEMI, PCI, or NSTEMI).
	• Offer clopidogrel as a treatment option for up to 12 months to people who have had an NSTEMI, regardless of treatment, or people who have had a STEMI and received a bare-metal or drug-eluting stent.
	• Offer clopidogrel as a treatment option for at least one month and consider continuing for up to 12 months in people who have had a STEMI and medical management with or without reperfusion treatment with a fibrinolytic agent.
	• Continue the second antiplatelet agent for up to 12 months in people who have had a STEMI and who received CABG surgery.
	• Offer clopidogrel instead of aspirin to people who also have other clinical vascular disease (had an MI and stopped dual antiplatelet therapy or had an MI more than 12 months ago).

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	Antiplatelet therapy in people with an indication for anticoagulation • Take bleeding risk, thromboembolic risk, and cardiovascular risk into account when deciding which people who have had an MI and have an indication for anticoagulation. • Unless there is a high risk of bleeding, continue anticoagulation and add aspirin to treatment in people who have had an MI who otherwise need anticoagulation and who have had their condition managed medically or have undergone balloon angioplasty or have undergone CABG surgery. • Continue anticoagulation and add clopidogrel to treatment in people who have had an MI, who have undergone PCI with bare-metal or drug-eluting stents and who otherwise need anticoagulation. • Offer clopidogrel with warfarin to people with a sensitivity to aspirin who otherwise need anticoagulation and aspirin and who have had an MI. • Do not routinely offer warfarin in combination with prasugrel or ticagrelor to people who need anticoagulation who have had an MI. • After 12 months since the MI, continue anticoagulation and take into consideration the need for ongoing antiplatelet therapy, taking into account all of the following: indication for anticoagulation, thromboembolic risk, bleeding risk, cardiovascular risk and the person's wishes. • Do not add a new oral anticoagulant (rivaroxaban, apixaban or dabigatran) in combination with dual antiplatelet therapy in people who otherwise need anticoagulation, who have had an MI. • Consider using warfarin and discontinuing treatment with a new oral anticoagulant (rivaroxaban, apixaban, or dabigatran) in people who otherwise need anticoagulation and who have had an MI, unless there is a specific clinical indication to continue it.
American College of Cardiology/American Heart Association: **Guideline for the Management of Heart Failure (2013)**[26]	Treatment of Stage A heart failure (HF) • Hypertension and lipid disorders should be controlled in accordance with guidelines to lower the risk of HF. (Level of Evidence (LoE): A) • Other conditions that may lead to or contribute to HF, such as obesity, diabetes mellitus, tobacco use, and known cardiotoxic agents, should be controlled or avoided. (LoE: C) Treatment of Stage B heart failure • In patients with a history of MI and reduced EF, ACE inhibitors or ARBs should be used to prevent HF. (LoE: A) • In patients with MI and reduced EF, evidence-based β-blockers (using one of three proven to reduce mortality [i.e., bisoprolol, carvedilol, and sustained-release metoprolol succinate]) should be used to prevent HF. (LoE: B) • In patients with MI, statins should be used to prevent HF. (LoE: A) • ACE inhibitors and β-blockers should be used in all patients with a reduced EF to prevent symptomatic HF, even if they do not have a history of MI. (LoE: A and C, respectively) • Blood pressure should be controlled to prevent symptomatic HF. (LoE: A) • Nondihydropyridine calcium channel blockers may be harmful in patients with low LVEF. (LoE: C) Pharmacological treatment for Stage C HFrEF • Recommendations for patients in Stages A and B are recommended where appropriate for patients in Stage C. (LoE: A, B, and C as appropriate) • Diuretics are recommended in patients with HFrEF who have evidence of fluid retention, unless contraindicated, to improve symptoms. (LoE: C) • ACE inhibitors are recommended in patients with HFrEF and current or prior

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	symptoms, unless contraindicated, to reduce morbidity and mortality. ARBs are recommended as alternative therapy in ACE inhibitor intolerant patients. (LoE: A) • Use of one of the three β-blockers proven to reduce mortality is recommended for all patients with current or prior symptoms of HFrEF, unless contraindicated, to reduce morbidity and mortality. (LoE: A) • Aldosterone receptor antagonists are recommended in patients with NYHA class II–IV HF and who have LVEF of ≤35%, unless contraindicated, to reduce morbidity and mortality. Patients with NYHA class II HF should have a history of prior cardiovascular hospitalization or elevated plasma natriuretic peptide levels to be considered for aldosterone receptor antagonists. Creatinine should be ≤2.5 mg/dL in men or ≤2.0 mg/dL in women (or estimated glomerular filtration rate >30 mL/min/1.73 m^2), and potassium should be <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) • The combination of hydralazine and isosorbide dinitrate is recommended to reduce morbidity and mortality for patients self-described as African Americans with NYHA class III–IV HFrEF receiving optimal therapy with ACE inhibitors and β-blockers, unless contraindicated. (LoE: A) • Digoxin can be beneficial in patients with HFrEF, unless contraindicated, to decrease hospitalizations for HF. (LoE: B) • Patients with chronic HF with permanent/persistent/paroxysmal AF and an additional risk factor for cardioembolic stroke (history of hypertension, diabetes mellitus, previous stroke or transient ischemic attack, or ≥75 years of age) should receive chronic anticoagulant therapy. (LoE: A) • Statins are not beneficial as adjunctive therapy when prescribed solely for the diagnosis of HF in the absence of other indications for their use. (LoE: A) • Calcium channel blockers are not recommended as routine treatment for patients with HFrEF. (LoE: A) <u>Pharmacological treatment for Stage C HFpEF</u> • Blood pressure should be controlled according to published clinical practice guidelines. (LoE: B) • Diuretics should be used for relief of symptoms due to volume overload. (LoE: C) • The use of β-blocking agents, ACE inhibitors, and ARBs in patients with hypertension is reasonable to control blood pressure in patients with HFpEF. (LoE: C) <u>Treatment of Stage D (advanced/refractory) HF</u> • Fluid restriction (1.5 to 2 L/d) is reasonable, especially in patients with hyponatremia, to reduce congestive symptoms. (LoE: C) • Until definitive therapy (e.g., coronary revascularization, mechanical circulatory support, heart transplantation) or resolution of the acute precipitating problem, patients with cardiogenic shock should receive temporary intravenous inotropic support to maintain systemic perfusion and preserve end-organ performance. (LoE: C) • Continuous intravenous inotropic support is reasonable as "bridge therapy" in patients with stage D HF refractory to medical therapy and device therapy who are eligible for and awaiting mechanical circulatory support or cardiac transplantation. (LoE: B) • Long-term use of either continuous or intermittent, intravenous parenteral positive inotropic agents, in the absence of specific indications or for reasons other than palliative care, is potentially harmful in the patient with HF. (LoE: B)
Heart Failure Society of America:	<u>Patients with left ventricular systolic dysfunction</u>

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Heart Failure Society of America 2010 Comprehensive Heart Failure Practice Guidelines (Executive Summary) (2010)[27]	• ACE inhibitors should be used in all patients with a LVEF ≤40%, unless otherwise contraindicated. • ARBs may be used in patients who are intolerant to ACE inhibitors. Hydralazine and a nitrate may be used in patients intolerant to ACE inhibitors and ARBs, or in whom such therapy is contraindicated. • The combination of an ACE inhibitor and a β-blocker is recommended in all patients with a LVEF ≤40%. • The routine use of an ARB with a combination of an ACE inhibitor and β-blocker in patients who have had a MI and have left ventricular dysfunction is not recommended. • The addition of an ARB can be considered in patients with heart failure due to reduced LVEF who have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor and a β-blocker. • Individual ARBs may be considered as initial therapy (instead of an ACE inhibitor) in patients with heart failure who have had a MI and in patients with chronic heart failure and systolic dysfunction. • ARBs are recommended in patients who cannot tolerate ACE inhibitors due to cough. The combination of hydralazine and an oral nitrate may be considered in such patients not tolerating ARB therapy. • Patients intolerant to ACE inhibitors from hyperkalemia or renal insufficiency are likely to experience the same side effects with ARBs. In these cases, the combination of hydralazine and an oral nitrate should be considered. • ARBs should be considered in patients experiencing angioedema while on ACE inhibitors based on their underlying risk and with recognition that angioedema has been reported infrequently with ARBs. The combination of hydralazine and oral nitrates may be considered in such patients not tolerating ARB therapy. • A combination of hydralazine and an oral nitrate is recommended in African American patients with heart failure and reduced left ventricular ejection fraction (LVEF) who are on a standard regimen of an ACE inhibitor (or ARB) and a β-blocker. • A combination of hydralazine and an oral nitrate may be considered in non–African American patients with heart failure and reduced LVEF who are symptomatic despite optimization of standard therapy. • Administration of an aldosterone antagonist is recommended for patients with New York Heart Association (NYHA) class IV (or class III, previously class IV) heart failure from reduced LVEF (<35%) while receiving standard therapy, including diuretics. • Administration of an aldosterone antagonist should be considered in patients following an acute MI, with clinical heart failure signs and symptoms or history of diabetes mellitus, and an LVEF <40%. Patients should be on standard therapy, including an ACE inhibitor (or ARB) and a β-blocker. • The triple combination of an ACE inhibitor, an ARB, and an aldosterone antagonist is not recommended because of the high risk of hyperkalemia. <u>Patients with hypertension and symptomatic left ventricular dysfunction with left ventricular dilation and low LVEF</u> • ACE inhibitors, ARBs, β-blockers, aldosterone inhibitors, and isosorbide dinitrate/hydralazine in various combinations (with a loop diuretic if needed) are recommended. • If blood pressure remains >130/80 mm Hg, a dihydropyridine calcium channel blocker (e.g., amlodipine or felodipine) may be considered or other antihypertensive medication doses increased. <u>Managing heart failure in special populations</u>

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	• The combination of hydralazine/isosorbide dinitrate is recommended for African American women with moderate to severe heart failure symptoms who are on background neurohormonal inhibition. • A combination of hydralazine and isosorbide dinitrate is recommended as part of standard therapy in addition to β-blockers and ACE-inhibitors for African Americans with left ventricular systolic dysfunction and NYHA class II-IV heart failure. • As in all patients, but especially in the elderly, careful attention to volume status, the possibility of symptomatic cerebrovascular disease and the presence of postural hypotension are recommended during therapy with ACE inhibitors, β-blockers and diuretics. <u>Patients with heart failure and preserved LVEF</u> • ACE inhibitors or ARBs should be considered in this patient population. • ACE inhibitors should be considered in patients with heart failure and symptomatic atherosclerotic cardiovascular disease or diabetes and at least one other risk factor. ARBs may be used in patients who are intolerant to ACE inhibitors. • Beta-blocker treatment is recommended in patients with HF and preserved LVEF who have prior MI, hypertension, or AF. • Calcium channel blockers should be considered in patients with heart failure and preserved LVEF who have atrial fibrillation requiring ventricular rate control and intolerance to β-blockers (consider diltiazem or verapamil), symptom-limiting angina, or hypertension. • Diuretic therapy is recommended in all patients with heart failure and clinical evidence of volume overload, including those with preserved LVEF. • Treatment may begin with either a thiazide or loop diuretic. In more severe volume overload or if response to a thiazide is inadequate, treatment with a loop diuretic should be implemented. • Excessive diuresis, which may lead to orthostatic changes in blood pressure and worsening renal function, should be avoided. <u>Patients with heart failure and CAD</u> • Calcium channel blockers should be considered in patients who have angina despite optimization of β-blocker and nitrates. Amlodipine and felodipine are preferred in patients with decreased systolic function. <u>Patients with heart failure and hypertension</u> • Patients with left ventricular hypertrophy or left ventricular dysfunction without left ventricular dilation should be treated to a goal blood pressure of <130/80 mm Hg. Treatment with several drugs may be necessary, including an ACE inhibitor (or ARB), a diuretic and a β-blocker or calcium channel blocker. • Patients with asymptomatic left ventricular dysfunction and left ventricular dilation and a reduced ejection fraction should receive an ACE inhibitor and a β-blocker. If blood pressure remains elevated (>130/80 mm Hg), the addition of a diuretic is recommended, followed by a calcium channel blocker or other antihypertensive agent. • If blood pressure remains >130/80 mm Hg, then the addition of a thiazide diuretic is recommended, followed by a dihydropyridine calcium channel blocker (e.g., amlodipine or felodipine) or other antihypertensive drugs. <u>Patients at risk for development of heart failure</u> • ACE inhibitors are recommended in patients who are at risk for the development of heart failure including patients with CAD, peripheral vascular disease, stroke, diabetes and another major risk factor, and patients with diabetes who smoke and

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	have microalbuminuria. <u>Patients with asymptomatic heart failure and reduced LVEF</u> • ACE inhibitors are recommended in asymptomatic patients with reduced LVEF (<40%). • ARBs may be used in patients who are intolerant to ACE inhibitors. • Routine use of a combination of ACE inhibitors and ARBs is not recommended. • β-blocker therapy should be considered. <u>Patients with heart failure and ischemic heart disease</u> • ACE inhibitor therapy is recommended in all patients with either reduced or preserved LVEF after a MI. • Beta-blockers are recommended for the management of all patients with reduced LVEF or post-MI. • ACE inhibitor and β-blocker therapy should be initiated early (<48 hours) during hospitalization in hemodynamically stable patients who are post-MI with reduced LVEF or heart failure. • Calcium channel blockers may be considered in patients with HF who have angina despite the optimal use of β-blockers and nitrates. <u>Managing heart failure in the elderly, women and African Americans</u> • Standard regimens of ACE inhibitors and β-blockers are recommended in elderly patients with heart failure. • ACE inhibitor and β-blocker therapy are recommended in all women with heart failure and left ventricular systolic dysfunction. • ACE inhibitor and β-blocker therapy are recommended in all African American patients with heart failure and left ventricular systolic dysfunction. ARBs may be substituted in patients who are intolerant to ACE inhibitors. <u>Heart failure in patients with reduced ejection fraction</u> • ACE inhibitors are recommended in asymptomatic patients with reduced LVEF (<40%). • ARBs may be used in patients who are intolerant to ACE inhibitors. • β-blockers shown to be effective in clinical trials of patients with heart failure are recommended for patients with a LVEF ≤40%. • The combination of a β-blocker and an ACE inhibitor is recommended as routine therapy for asymptomatic patients with a LVEF ≤40%. The evidence is stronger in patients with a history of MI. • β-blocker therapy is recommended for patients with a recent decompensation of heart failure after optimization of volume status and successful discontinuation of intravenous diuretics and vasoactive drugs. Whenever possible, β-blocker therapy should be initiated in the hospital setting at a low dose prior to discharge of stable patients. • β-blocker therapy is recommended in the great majority of patients with heart failure and reduced LVEF, even if there is concurrent diabetes, chronic obstructive pulmonary disease or peripheral vascular disease. Caution may be warranted in these patients. • It is recommended that β blockade be initiated at low doses and uptitrated gradually. • It is recommended that β-blocker therapy be continued in most patients experiencing a symptomatic exacerbation of heart failure during chronic maintenance treatment, unless they develop cardiogenic shock, refractory volume overload or symptomatic bradycardia. • The routine use of an ARB is not recommended in addition to an ACE inhibitor

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	and a β-blocker in patients with a recent acute MI and reduced LVEF. • The addition of an ARB should be considered in patients with heart failure due to reduced LVEF who have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor and a β-blocker. • Administration of an aldosterone antagonist is recommended for patients with NYHA class IV (or class III, previously class IV) HF from reduced LVEF (<35%) while receiving standard therapy, including diuretics. • Diuretic therapy is recommended to restore and maintain normal volume status in patients with clinical evidence of fluid overload, generally manifested by congestive symptoms or signs of elevated filling pressures. Loop diuretics rather than thiazide-type diuretics are typically necessary to restore normal volume status in patients with heart failure. • The initial dose of diuretic may be increased as necessary to relieve congestion, and restoration of normal volume status may require multiple adjustments, especially in patients with severe fluid overload evidenced by massive edema or ascites. After a diuretic effect is achieved with loop diuretics (short acting), increasing administration frequency to twice or even three times/day will provide more diuresis with less physiologic perturbation than larger single doses. • Oral torsemide may be considered in patients in whom poor absorption of oral medication or erratic diuretic effect may be present. Particularly in patients with right-sided heart failure and refractory fluid retention despite high doses of other loop diuretics. • Intravenous administration of diuretics may be necessary to relieve congestion. • Diuretic refractoriness may represent patient nonadherence, a direct effect of diuretic use on the kidney or progression of underlying cardiac dysfunction. • Addition of chlorothiazide or metolazone, once or twice daily, to loop diuretics should be considered in patients with persistent fluid retention despite high dose loop diuretic therapy. Chronic daily use should be avoided if possible because of the potential for electrolyte shifts and volume depletion. These drugs may be used periodically (every other day or weekly) to optimize fluid management. Metolazone will generally be more potent and much longer acting in this setting and in patients with chronic renal insufficiency, so administration should be adjusted accordingly. Volume status and electrolytes must be monitored closely when multiple diuretics are used. • Careful observation for the development of side effects is recommended in patients treated with diuretics, especially when high doses or combination therapy are used. Patients should undergo routine laboratory studies and clinical examination as dictated by their clinical response. • Patients requiring diuretic therapy to treated fluid retention associated with heart failure generally require chronic treatment, although often at lower doses than those required initially to achieve diuresis. Decreasing or discontinuing therapy may be considered in patients experiencing significant improvement in clinical status and cardiac function or in those who successfully restrict dietary sodium intake. These patients may undergo cautious weaning of diuretic dose and frequency with careful observation for recurrent fluid retention. • Patients and caregivers should be given education on the early signs of fluid retention and the plan for initial therapy. • Selected patients may be educated to adjust daily dose of diuretic in response to weight gain from fluid overload. <u>Evaluation and management of patients with acute decompensated heart failure</u> • Patients admitted with acute decompensated heart failure and evidence of fluid overload be treated initially with loop diuretics; usually given intravenously rather than orally. Ultrafiltration may be considered in lieu of diuretics. • Diuretics should be administered at doses needed to produce a rate of diuresis

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	sufficient to achieve optimal volume status with relief of signs and symptoms of congestion, without inducing an excessively rapid reduction in intravascular volume or serum electrolytes.
	• Monitoring of daily weights, intake and output is recommended to assess clinical efficacy of diuretic therapy.
	• Careful observation for development of a variety of side effects, including renal dysfunction, electrolyte abnormalities, symptomatic hypotension and gout is recommended in patients treated with diuretics, especially when high doses or combination therapy is used.
	• Careful observation for the development of renal dysfunction is recommended in patients treated with diuretics. Patients with moderate to severe renal dysfunction and evidence of fluid retention should continue to be treated with diuretics. In the presence of severe fluid overload, renal dysfunction may improve with diuresis.
	• When congestion fails to improve in response to diuretic therapy, the following options should be considered:
	  ○ Re-evaluating the presence/absence of congestion.
	  ○ Sodium and fluid restriction.
	  ○ Increasing doses of loop diuretic.
	  ○ Continuous infusion of a loop diuretic.
	  ○ Addition of a second type of diuretic orally (metolazone or spironolactone) or intravenously (chlorothiazide).
	  ○ Ultrafiltration may be considered as well.

European Society of Cardiology: **Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (2016)**[28]	Pharmacological treatments indicated in patients with symptomatic (NYHA Class II-IV) heart failure with reduced ejection fraction • An ACE inhibitor is recommended, in addition to a beat-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death. • A mineralocorticoid receptor antagonist 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. • Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion. • 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. • 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. • 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

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	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). Recommendations for treatment of patients with heart failure with preserved ejection fraction and heart failure with mid-range ejection fraction • It is recommended to screen patients with HFpEF or HFmrEF (mid-range) 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 or HFmrEF in order to alleviate symptoms and signs. Recommendations for initial management of a rapid ventricular rate in patients with heart failure and atrial fibrillation in the acute or chronic setting • Urgent electrical cardioversion is recommended if AF is thought to be contributing to the patient's hemodynamic compromise in order to improve the patient clinical condition. • For patients in NYHA Class IV, in addition to treatment for acute HF, an intravenous bolus of amiodarone or, in digoxin-naïve patients, an intravenous bolus of digoxin should be considered to reduce the ventricular rate. • For patients in NYHA Class I–III, a β-blocker, usually given orally, is safe and therefore is recommended as first-line treatment to control ventricular rate, provided the patient is euvolemic. • For patients in NYHA Class I–III, digoxin should be considered when ventricular rate remains high despite β-blockers or when β-blockers are not tolerated or contraindicated. • Treatment with dronedarone to improve ventricular rate control is not recommended due to safety concerns. Recommendations for cardiac imaging in patients with suspected or established heart failure • Transthoracic Echocardiogram (TTE) is recommended for the assessment of myocardial structure and function in subjects with suspected HF in order to establish a diagnosis of HFrEF, HFmrEF, or HFpEF. • TTE is recommended for the assessment of LVEF in order to identify patients with HF who would be suitable for evidence-based pharmacological and device treatment recommended for HFrEF. Recommendations aiming to prevent or delay the development of overt heart failure or prevent death before the onset of symptoms • Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life. • ACE inhibitor is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction in order to prevent or delay the onset of HF and prolong life. • Beta-blocker is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction, in order to prevent or delay the onset of HF and prolong life.

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	Pharmacological treatments indicated in patients with symptomatic 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 β-blocker is recommended, in addition to an ACE inhibitor, for patients with stable, symptomatic HFrEF to reduce the risk of HF hospitalization and death. • A mineralocorticoid receptor antagonist 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. Other pharmacological treatments recommended in selected patients with symptomatic heart failure with reduced ejection fraction • Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion. • 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. Treatments (or combinations of treatments) that may cause harm in patients with symptomatic (New York Heart Association Class II–IV) heart failure with reduced ejection fraction • Diltiazem or verapamil are not recommended in patients with HFrEF, as they increase the risk of HF worsening and HF hospitalization. • The addition of an ARB (or a renin inhibitor) to the combination of an ACE inhibitor and a mineralocorticoid receptor antagonist is not recommended in patients with HF, because of the increased risk of renal dysfunction and hyperkalemia. Not-recommended treatments of co-morbidities in patients with heart failure • Thiazolidinediones (glitazones) are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization. • NSAIDs or COX-2 inhibitors are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization. Recommendations for the 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. • In patients with new-onset AHF or those with chronic, decompensated HF not receiving oral diuretics the initial recommended dose should be 20 to 40 mg intravenous furosemide (or equivalent); for those on chronic diuretic therapy, initial intravenous dose should be at least equivalent to oral dose. • It is recommended to give diuretics either as intermittent boluses or a continuous infusion, and the dose and duration should be adjusted according to the patients' symptoms and clinical status. • Inotropic agents are not recommended unless the patient is symptomatically hypotensive or hypoperfused because of safety concern.
Eighth Joint National Committee (JNC 8): **2014 Evidence-**	• 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

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based Guideline for the Management of High Blood Pressure in Adults (2014)[29]	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.
American Society of Hypertension/ International Society of Hypertension: **Clinical Practice Guidelines for the Management of Hypertension in the Community (2014)[30]**	Nonpharmacologic treatment • In patients with hypertension that is no more severe than stage one and is not associated with evidence of abnormal cardiovascular findings or other cardiovascular risks, six to 12 months of lifestyle changes can be attempted in the hope that they may be sufficiently effective to make it unnecessary to use medicines. • It may be prudent to start treatment with drugs sooner if it is clear that the blood pressure is not responding to the lifestyle methods or if other risk factors appear. • Weight loss: In patients who are overweight or obese, weight loss is helpful in treating hypertension, diabetes, and lipid disorders. • Salt reduction: Reduction of salt intake is recommended because it can reduce blood pressure and decrease the need for medications in patients who are "salt sensitive." • Exercise: Regular aerobic exercise can help reduce blood pressure. • Alcohol consumption: Up to two drinks a day can be helpful in protecting against cardiovascular events, but greater amounts of alcohol can raise blood pressure and should therefore be discouraged. In women, alcohol should be limited to one drink a day. • Cigarette smoking: Stopping smoking will not reduce blood pressure, but since smoking by itself is such a major cardiovascular risk factor, patients must be

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	strongly urged to discontinue this habit.
	
	Drug treatment of hypertension
	• Treatment with drugs should be started in patients with blood pressures >140/90 mm Hg in whom lifestyle treatments have not been effective.
	• In patients with stage two hypertension (blood pressure ≥160/100 mm Hg), drug treatment should be started immediately after diagnosis, usually with a two-drug combination, without waiting to see the effects of lifestyle changes.
	• For patients older than 80 years, the suggested threshold for starting treatment is at levels ≥150/90 mm Hg. Thus, the target of treatment should be <140/90 mm Hg for most patients but <150/90 mm Hg for older patients (unless these patients have chronic kidney disease or diabetes, when <140/90 mm Hg can be considered).
	• Most patients will require more than one drug to achieve control of their blood pressure.
	• In general, increase the dose of drugs or add new drugs at approximately two to three week intervals. This frequency can be faster or slower depending on the judgment of the practitioner. In general, the initial doses of drugs chosen should be at least half of the maximum dose so that only one dose adjustment is required thereafter. It is generally anticipated that most patients should reach an effective treatment regimen, whether one, two, or three drugs, within six to eight weeks.
	• Choice of drugs should be influenced by the age, ethnicity/race, and other clinical characteristics of the patient.
	• The choice of drugs will also be influenced by other conditions (e.g., diabetes and coronary disease) associated with the hypertension. Pregnancy also influences drug choice.
	• Long-acting drugs that need to be taken only once daily are preferred to shorter-acting drugs that require multiple doses because patients are more likely to follow a simple treatment regimen.
	• This guideline only makes recommendations for drug classes, not individual agents. There is an assumption, unless otherwise stated, that all drugs in a class are similar to each other.
	• Drug selectin when hypertension is the only or main concern:
	  ○ For black patients of all ages, use calcium channel blocker (CCB) or thiazide diuretic as first drug, then add angiotensin receptor blocker (ARB) or angiotensin-converting enzyme (ACE) inhibitor if needed.
	  ○ For white and other non-black patients <60 years of age, use ARB or ACE inhibitor as first drug, then add CCB or thiazide diuretic if needed.
	  ○ For white and other non-black patients ≥60 years of age, use CCB or thiazide diuretic as first drug, then add ARB or ACE inhibitor if needed.
	• Drug selection when hypertension is associated with other conditions:
	  ○ For patients with hypertension and diabetes, use ARB or ACE inhibitor as first drug (note, in black patients it is acceptable to start with a CCB or thiazide), then add CCB or thiazide diuretic (unless starting on CCB or thiazide in black patients) if needed.
	  ○ For patients with hypertension and chronic kidney disease, use ARB or ACE inhibitor as first drug, then add CCB or thiazide diuretic if needed.
	  ○ For patients with hypertension and clinical coronary artery disease, use β-blocker plus ARB or ACE inhibitor as first drugs, then add CCB or thiazide diuretic if needed.
	  ○ For patients with hypertension and stroke history, use ACE inhibitor or ARB as first drug, then add thiazide diuretic or CCB if needed.
	• For patients with hypertension and heart failure, patients with h symptomatic heart failure should usually receive an ARB or ACE inhibitor plus β-blocker plus diuretic plus spironolactone regardless of blood pressure. A dihydropyridine CCB can be added if needed for blood pressure control.

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Hypertension Canada: **2017 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults (2017)**[31]	<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.
	
	<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>Guidelines for individuals 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.

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	• 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 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. Treatment of hypertension in association with stroke

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	• BP management in acute ischemic stroke (onset to 72 hours)
	  ○ For patients with ischemic stroke not eligible for thrombolytic therapy, treatment of hypertension in the setting of acute ischemic stroke or transient ischemic attack should not be routinely undertaken. Extreme BP increases (e.g., SBP >220 mmHg or DBP >120 mmHg) may be treated to reduce the BP by approximately 15%, and not more than 25%, over the first 24 hours with gradual reduction thereafter. Avoid excessive lowering of BP because this might exacerbate existing ischemia or might induce ischemia, particularly in the setting of intracranial arterial occlusion or extracranial carotid or vertebral artery occlusion. Pharmacological agents and routes of administration should be chosen to avoid precipitous decreases in BP.
	  ○ For patients with ischemic stroke eligible for thrombolytic therapy, very high BP (>185/110 mmHg) should be treated concurrently in patients receiving thrombolytic therapy for acute ischemic stroke to reduce the risk of secondary intracranial hemorrhage.
	• 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)
	  ○ For patients with intracerebral hemorrhage (ICH) in the hyperacute phase (in the first 24 hours) SBP lowering to <140 mmHg should be avoided because of an absence of benefit (relative to a target of <180 mmHg) and some suggestion of harm.
	
	<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>
	• For patients with nondiabetic chronic kidney disease, target BP is <140/90 mmHg.
	• For patients with hypertension and proteinuric chronic kidney disease (urinary protein >500 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.
	• Thiazide/thiazide-like diuretics are recommended as additive antihypertensive therapy. For patients with chronic kidney disease and volume overload, loop diuretics are an alternative.
	• 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

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	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. • In patients with hypertension attributable to FMD-related renal artery stenosis, revascularization should be considered. • 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 2 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. Combination therapy using two first-line agents may also be considered as initial treatment of hypertension if SBP is 20 mmHg greater than target or if DBP is 10 mmHg greater than target. However, caution should be exercised in patients in whom a substantial decrease in BP is more likely or poorly tolerated (e.g., elderly patients and patients with autonomic neuropathy). • 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.
European Society of Hypertension/European Society of Cardiology: **2013 Guidelines for the management of arterial hypertension (2013)**[32]	The 2013 guidelines on hypertension of the European Society of Hypertension and the European Society of Cardiology follow the guidelines jointly issued by the two societies in 2003 and 2007. <u>Treatment strategies and choice of antihypertensive drugs</u> • Diuretics (including thiazides, chlorthalidone, and indapamide), β-blockers, calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) are all suitable for the initiation and maintenance of antihypertensive treatment, either as monotherapy or in some combinations. • Some agents should be considered as the preferential choice in specific conditions because used in trials in those conditions or because of greater effectiveness in specific types of organ damage. • Initiation of antihypertensive therapy with a two-drug combination may be considered in patients with markedly high baseline blood pressure (BP) or at high cardiovascular (CV) risk. • The combination of two antagonists of the renin-angiotensin system (RAS) is not recommended and should be discouraged. • Other drug combinations should be considered and probably are beneficial in proportion to the extent of BP reduction. However, combinations that have been successfully used in trials may be preferable. • Combinations of two antihypertensive drugs at fixed doses in a single tablet may be recommended and favored, because reducing the number of daily pills

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	improves adherence, which is low in patients with hypertension. Treatment strategies in white-coat and masked hypertension • In white-coat hypertensives without additional risk factors, therapeutic intervention may be limited to lifestyle changes only, but this decision should be accompanied by close follow-up. • In white-coat hypertensives with a higher CV risk because of metabolic derangements or asymptomatic organ damage, drug treatment may be considered in addition to lifestyle changes. • In masked hypertension, both lifestyle measures and antihypertensive drug treatment should be considered, because this type of hypertension has been consistently found to have a CV risk very close to that of in- and out-of-office hypertension. Antihypertensive treatment strategies in the elderly • In elderly hypertensives with SBP ≥160 mmHg there is solid evidence to recommend reducing SBP to between 150 and 140 mmHg. • In fit elderly patients <80 years old antihypertensive treatment may be considered at SBP values ≥140 mmHg with a target SBP <140 mmHg if treatment is well tolerated. • In individuals older than 80 years with an initial SBP ≥160 mmHg, it is recommended to reduce SBP to between 150 and 140 mmHg, provided they are in good physical and mental conditions. • In frail elderly patients, it is recommended to leave decisions on antihypertensive therapy to the treating physician, and based on monitoring of the clinical effects of treatment. • Continuation of well-tolerated antihypertensive treatment should be considered when a treated individual becomes an octogenarian. • All hypertensive agents are recommended and can be used in the elderly, although diuretics and calcium antagonists may be preferred in isolated systolic hypertension. Treatment strategies in hypertensive women • Hormone therapy and selective estrogen receptor modulators are not recommended and should not be used for primary or secondary prevention of CVD. • If treatment of younger perimenopausal women is considered for severe menopausal symptoms, the benefits should be weighed against potential risks. • Drug treatment of severe hypertension in pregnancy (SBP >160 mmHg or DBP >110 mmHg) is recommended. • Drug treatment may also be considered in pregnant women with persistent elevation of BP ≥150/95 mmHg, and in those with BP ≥140/90 mmHg in the presence of gestational hypertension, subclinical organ damage or symptoms. • In women at high risk of pre-eclampsia, provided they are at low risk of gastrointestinal hemorrhage, treatment with low dose aspirin from 12 weeks until delivery may be considered. • In women with child-bearing potential RAS blockers are not recommended and should be avoided. • Methyldopa, labetalol, and nifedipine should be considered preferential antihypertensive drugs in pregnancy. Intravenous labetalol or infusion of nitroprusside should be considered in case of emergency (pre-eclampsia). Treatment strategies in patients with diabetes • While initiation of antihypertensive drug treatment in diabetic patients whose SBP

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	is ≥160 mmHg is mandatory, it is strongly recommended to start drug treatment also when SBP is ≥140 mmHg. • A SBP goal <140 mmHg is recommended in patients with diabetes. • The DBP target in patients with diabetes is recommended to be <85 mmHg. • All classes of antihypertensive agents are recommended and can be used in patients with diabetes; RAS blockers may be preferred, especially in the presence of proteinuria or microalbuminuria. • It is recommended that individual drug choice takes comorbidities into account. • Simultaneous administration of two blockers of the RAS is not recommended and should be avoided in patients with diabetes <u>Treatment strategies in hypertensive patients with metabolic syndrome</u> • Lifestyle changes, particularly weight loss and physical exercise, are to be recommended to all individuals with the metabolic syndrome. These interventions improve not only BP, but the metabolic components of the syndrome and delay diabetes onset. • As the metabolic syndrome can be considered a 'pre-diabetic' state, antihypertensive agents potentially improving or at least not worsening insulin sensitivity, such as RAS blockers and calcium antagonists, should be considered as the preferred drugs. Beta-blockers (with the exception of vasodilating β-blockers) and diuretics should be considered only as additional drugs, preferably in association with a potassium-sparing agent. • It is recommended to prescribe antihypertensive drugs with particular care in hypertensive patients with metabolic disturbances when BP is ≥140/90 mmHg after a suitable period of lifestyle changes, and to maintain BP <140/90 mmHg. • BP lowering drugs are not recommended in individuals with metabolic syndrome and high normal BP. <u>Therapeutic strategies in hypertensive patients with nephropathy</u> • Lowering SBP to <140 mmHg should be considered. • When overt proteinuria is present, SBP values <130 mmHg may be considered, provided that changes in eGFR are monitored. • RAS blockers are more effective in reducing albuminuria than other antihypertensive agents, and are indicated in hypertensive patients in the presence of microalbuminuria or overt proteinuria. • Reaching BP goals usually requires combination therapy, and it is recommended to combine RAS blockers with other antihypertensive agents. • Combination of two RAS blockers, though potentially more effective in reducing proteinuria, is not recommended. • Aldosterone antagonists cannot be recommended in chronic kidney disease (CKD), especially in combination with a RAS blocker, because of the risk of excessive reduction in renal function and of hyperkalemia. <u>Therapeutic strategies in hypertensive patients with cerebrovascular disease</u> • It is not recommended to intervene with BP-lowering therapy during the first week after acute stroke irrespective of BP level, although clinical judgement should be used in the face of very high SBP values. • Antihypertensive treatment is recommended in hypertensive patients with a history of stroke or transient ischemic attack (TIA), even when initial SBP is in the 140 to 159 mmHg range. • In hypertensive patients with a history of stroke or TIA, a SBP goal of <140 mmHg should be considered. • In elderly hypertensives with previous stroke or TIA, SBP values for intervention and goal may be considered to be somewhat higher.

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	• All drug regimens are recommended for stroke prevention, provided that BP is effectively reduced. Therapeutic strategies in hypertensive patients with heart disease • In hypertensive patients with CHD, a SBP goal <140 mmHg should be considered. • In hypertensive patients with a recent myocardial infarction, β-blockers are recommended. In case of other CHD all antihypertensive agents can be used, but β-blockers and calcium antagonists are to be preferred for symptomatic reasons (angina). • Diuretics, β-blockers, ACE inhibitors, angiotensin receptor blockers, and/or mineralocorticoid receptor antagonists are recommended in patients with heart failure or severe left ventricular (LV) dysfunction to reduce mortality and hospitalization. • In patients with heart failure and preserved ejection fraction (EF), there is no evidence that antihypertensive therapy per se or any particular drug is beneficial. However, in these patients, as well as in patients with hypertension and systolic dysfunction, lowering SBP to around 140 mmHg should be considered. Treatment guided by relief of symptoms (congestion with diuretics, high heart rate with β-blockers, etc.) should also be considered. • ACE inhibitors and angiotensin receptor blockers (and β-blockers and mineralocorticoid receptor antagonists if heart failure coexists) should be considered as antihypertensive agents in patients at risk of new or recurrent atrial fibrillation. • It is recommended that all patients with left ventricular hypertrophy (LVH) receive antihypertensive agents. • In patients with LVH, initiation of treatment with one of the agents that have shown a greater ability to regress LVH should be considered, i.e. ACE inhibitors, angiotensin receptor blockers, and calcium antagonists. Therapeutic strategies in hypertensive patients with atherosclerosis, arteriosclerosis, and peripheral artery disease (PAD) • In the presence of carotid atherosclerosis, prescription of calcium antagonists and ACE inhibitors should be considered as these agents have shown a greater efficacy in delaying atherosclerosis progression than diuretics and β-blockers. • In hypertensive patients with a pulse wave velocity above 10 m/s, all antihypertensive drugs should be considered provided that a BP reduction to <140/90 mmHg is consistently achieved. • Antihypertensive therapy is recommended in hypertensive patients with PAD to achieve a goal of <140/90 mmHg, because of their high risk of myocardial infarction, stroke, heart failure, and CV death. • Though a careful follow up is necessary, β-blockers may be considered for the treatment of arterial hypertension in patients with PAD, since their use does not appear to be associated with exacerbation of PAD symptoms.
National Institute for Health and Clinical Excellence: **Hypertension in adults: diagnosis and management (2011)**[33] **Reaffirmed Nov 2016**	Choosing antihypertensive drug treatment • 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 people ≥80 years of age the same antihypertensive drug treatment as people aged 55 to 80 years, taking into account any comorbidities. • Offer antihypertensive drug treatment to women of child-bearing potential in line with the recommendations on Management of pregnancy with chronic hypertension and Breastfeeding in 'Hypertension in pregnancy' (NICE clinical

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	guideline 107).
	
	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). 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 step one antihypertensive (ACE inhibitor, ARB) with a calcium channel blocker (CCB) to patients >55 years of age and to black patients of African or Caribbean family origin 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 chlorthalidone (12.5 to 25.0 mg once daily) or indapamide (1.5 mg modified-release once daily or 2.5 mg once daily) in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide.
	• For patients who are already receiving treatment with bendroflumethiazide or hydrochlorothiazide and whose blood pressure is stable and well controlled, continue treatment as is.
	• β-blockers are not a preferred initial therapy for hypertension; however, β-blockers may be considered in younger patients, particularly:
	  ○ Patients with an intolerance or contraindication to ACE inhibitors and ARBs.
	  ○ Women of child-bearing potential.
	  ○ People with evidence of increased sympathetic drive.
	• If treatment is initiated with a β-blocker and a second antihypertensive is required, add a CCB over a thiazide-like diuretic to reduce the risk of developing diabetes.
	
	Step two treatment
	• If blood pressure is not controlled with a step one antihypertensive, offer a step two treatment with a CCB in combination with an ACE inhibitor or an ARB.
	• If a CCB is not appropriate or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic.
	• For black patients of African or Caribbean family origin, consider an ARB in preference to an ACE inhibitor, in combination with a CCB.
	
	Step three treatment
	• Before considering step three treatment, review medication to ensure step two treatment is at optimal or best tolerated doses.
	• If three drugs are required to control blood pressure, the combination of an ACE inhibitor or ARB, CCB, and thiazide-like diuretic should be utilized.
	
	Step four treatment
	• Regard clinic blood pressure that remains >140/90 mmHg after treatment with the optimal or best tolerated doses of an ACE inhibitor or an ARB plus a CCB plus a diuretic as resistant hypertension, and consider adding a fourth antihypertensive drug and/or seeking expert advice.
	• For treatment of resistant hypertension at step four:
	  ○ Consider further diuretic therapy with low-dose spironolactone (25 mg once daily) if the blood potassium level is 4.5 mmol/l or lower. Use particular caution in people with a reduced estimated glomerular filtration rate because they have an increased risk of hyperkalemia.
	  ○ Consider higher-dose thiazide-like diuretic treatment if the blood potassium level is higher than 4.5 mmol/l.
	  ○ If further diuretic therapy for resistant hypertension is not tolerated or is

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	contraindicated or ineffective, consider an α-blocker or β-blocker.
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 (2012)**[35]	<u>Blood pressure management in chronic kidney disease (CKD) non-dialysis (ND) patients without diabetes mellitus</u> • The Work Group recommends that non-diabetic adults with CKD ND and urine albumin excretion <30 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >140 mm Hg systolic or >90 mm Hg diastolic be treated with blood pressure -lowering drugs to maintain a blood pressure that is consistently ≤140 mm Hg systolic and ≤90 mm Hg diastolic. • The Work Group suggests that non-diabetic adults with CKD ND and urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with BP-lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic. • The Work Group suggests that non-diabetic adults with CKD ND and urine albumin excretion >300 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with blood pressure -lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤ 80 mm Hg diastolic. • The Work Group suggests that an angiotensin receptor blocker (ARB) or angiotensin converting enzyme inhibitor (ACE-I) be used in non-diabetic adults with CKD ND and urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*) in whom treatment with blood pressure -lowering drugs is indicated. • The Work Group recommends that an ARB or ACE-I be used in non-diabetic adults with CKD ND and urine albumin excretion >300 mg per 24 hours (or equivalent*) in whom treatment with blood pressure -lowering drugs is indicated. <u>Blood pressure management in CKD ND patients with diabetes mellitus</u> • The Work Group recommends that adults with diabetes and CKD ND with urine albumin excretion <30 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >140 mm Hg systolic or >90 mm Hg diastolic be treated with BP-lowering drugs to maintain a blood pressure that is consistently ≤140 mm Hg systolic and ≤90 mm Hg diastolic.

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	• The Work Group suggests that adults with diabetes and CKD ND with urine albumin excretion >30 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with BP-lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic. • The Work Group suggests that an ARB or ACE-I be used in adults with diabetes and CKD ND with urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*). • The Work Group recommends that an ARB or ACE-I be used in adults with diabetes and CKD ND with urine albumin excretion >300 mg per 24 hours (or equivalent*). <u>Blood pressure management in kidney transplant recipients (non–dialysis-dependent CKD of any stage with a kidney transplant [CKD T])</u> • The Work Group suggests that adult kidney transplant recipients whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic, irrespective of the level of urine albumin excretion. • In adult kidney transplant recipients, choose a blood pressure -lowering agent after taking into account the time after transplantation, use of calcineurin inhibitors, presence or absence of persistent albuminuria, and other co morbid conditions. <u>Blood pressure management in children with CKD ND</u> • The Work Group recommends that in children with CKD ND, blood pressure -lowering treatment is started when blood pressure is consistently above the 90th percentile for age, sex, and height. • The Work Group suggests that in children with CKD ND (particularly those with proteinuria), blood pressure is lowered to consistently achieve systolic and diastolic readings less than or equal to the 50th percentile for age, sex, and height, unless achieving these targets is limited by signs or symptoms of hypotension. • The Work Group suggests that an ARB or ACE-I be used in children with CKD ND in whom treatment with blood pressure -lowering drugs is indicated, irrespective of the level of proteinuria. <u>Blood pressure management in elderly persons with CKD ND</u> • Tailor blood pressure treatment regimens in elderly patients with CKD ND by carefully considering age, co-morbidities and other therapies, with gradual escalation of treatment and close attention to adverse events related to blood pressure treatment, including electrolyte disorders, acute deterioration in kidney function, orthostatic hypotension and drug side effects. *Approximate equivalents for albumin excretion rate per 24 hours is expressed as protein excretion rate per 24 hours, albumin/creatinine ratio, protein/creatinine ratio, and protein reagent strip results.
American Diabetes Association: **Standards of Medical Care in Diabetes (2017)**[36]	<u>Hypertension/blood pressure control</u> • Blood pressure should be measured at every routine visit. Patients found to have elevated blood pressure should have blood pressure confirmed on a separate day. • Most patients with diabetes and hypertension should be treated to a systolic blood pressure goal of <140 mmHg and a diastolic blood pressure goal of <90 mmHg. • Lower systolic and diastolic blood pressure targets, such as 130/80 mmHg, may be appropriate for individuals at high risk of cardiovascular disease, if they can be achieved without undue treatment burden. • In pregnant patients with diabetes and chronic hypertension, blood pressure targets of 120 to 160/80 to 105 mmHg are suggested in the interest of optimizing long-term maternal health and minimizing impaired fetal growth.

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	• Patients with confirmed office-based blood pressure >140/90 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). 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. • For patients with blood pressure >120/80 mmHg, lifestyle intervention consists of weight loss if overweight or obese; a Dietary Approaches to Stop Hypertension–style dietary pattern including reducing sodium and increasing potassium intake; moderation of alcohol intake; and increased physical activity. <u>Coronary heart disease</u> • In asymptomatic patients, routine screening for coronary artery disease is not recommended as it does not improve outcomes as long as atherosclerotic cardiovascular disease risk factors are treated. • Consider investigations for coronary artery disease in the presence of any of the following: atypical cardiac symptoms (e.g., unexplained dyspnea, chest discomfort); signs or symptoms of associated vascular disease including carotid bruits, transient ischemic attack, stroke, claudication, or peripheral arterial disease; or electrocardiogram abnormalities (e.g., Q waves). • In patients with known atherosclerotic cardiovascular disease, use aspirin and statin therapy (if not contraindicated) and consider ACE inhibitor therapy to reduce the risk of cardiovascular events. • In patients with prior myocardial infarction, β-blockers should be continued for at least two years after the event. • In patients with symptomatic heart failure, thiazolidinedione treatment should not be used. • In patients with type 2 diabetes with stable congestive heart failure, metformin may be used if estimated glomerular filtration remains >30 mL/min but should be avoided in unstable or hospitalized patients with congestive heart failure. <u>Diabetic 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, in all patients with type 2 diabetes, and in all patients with comorbid hypertension. • Optimize glucose control to reduce the risk or slow the progression of diabetic kidney disease. • Optimize blood pressure control to reduce the risk or slow the progression of diabetic kidney disease.

Clinical Guideline	Recommendations
	• For people with nondialysis-dependent diabetic kidney disease, dietary protein intake should be approximately 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. • 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) B 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 or changes in potassium when ACE inhibitors, angiotensin receptor blockers, or diuretics are used. • Continued monitoring of urinary albumin–to–creatinine ratio in patients with albuminuria treated with an ACE inhibitor or an angiotensin receptor blocker is reasonable to assess the response to treatment and progression of diabetic kidney disease. • An ACE inhibitor or an angiotensin receptor blocker is not recommended for the primary prevention of diabetic kidney disease 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. • When estimated glomerular filtration rate is <60 mL/min/1.73 m^2, evaluate and manage potential complications of chronic kidney disease. • Patients should be referred for evaluation for renal replacement treatment if they have an estimated glomerular filtration rate <30 mL/min/1.73 m^2. • Promptly refer to a physician experienced in the care of kidney disease 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 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[1,6-17]

Indication(s)	Single Entity Agents							Combination Products				
	Amlo-dipine	Felo-dipine	Isra-dipine	Nicar-dipine	Nife-dipine	Nimo-dipine	Nisol-dipine	Amlodipine and Benazepril	Amlodipine and Olmesartan	Amlodipine and Perindopril	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, ER tablet)							
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.
**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) Feces (20 to 25)	30 to 60
Felodipine	13 to 20	>99	Liver, extensive	Renal (70) Feces (10)	11 to 16
Isradipine	14 to 24	95 to 97	Liver, complete	Renal (60 to 65) Feces (30)	8
Nicardipine	35	>95	Liver, nearly 100%	Renal (60) Feces (35)	8 to 12
Nifedipine	IR: rapid and complete ER: 84 to 89	92 to 98	Liver, extensive	Renal (80) Feces (20)	2
Nimodipine	13	>95	Liver, extensive	Renal (% not reported) Feces (% not reported)	1 to 2
Nisoldipine	5	>99	Liver, extensive	Renal (60 to 80) Feces (6 to 12)	7 to 12
Combination Products					
Amlodipine and benazepril	64 to 90/≥37	93/93	Liver, extensive (90)/ Liver, extensive (% not reported)	Renal (60)/ Renal (20) Feces (11 to 12)	48/ 10 to 11
Amlodipine and olmesartan	64 to 90/26	93/99	Liver, extensive (90)/ Intestinal wall (100)	Renal (60)/ Renal (35 to 50) Feces (50 to 65)	45/7
Amlodipine and perindopril	64 to 90/75	93/60	Liver, extensive (90)/ Liver, extensive	Renal (60)/ Renal (4 to 12)	30 to 50/ 0.8 to 1 (120 for active metabolite)
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/ 50 to 75	93/ 95/ 40 to 68	Liver, extensive (90)/ Liver, minimal (20)/ Not metabolized	Renal (60)/ Renal (7 to 13) Feces (83)/ Renal (>61)	45/ 6 to 9/ 6 to 15

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

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	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)	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, 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).
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, nimodipine)	HCV protease inhibitors	Dihydropyridine serum levels may increase resulting from a decrease metabolism due to CYP3A4 inhibition by protease inhibitors.
Dihydropyridines (amlodipine, 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)	ACE Inhibitors	Coadministration of ARBs and ACE inhibitors may be 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,	Clopidogrel	Concurrent use may result in decreased antiplatelet effect and increased risk of thrombotic events.

Generic Name(s)	Interaction	Mechanism
nisoldipine)		
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 may be increased when aliskiren is coadministered with benazepril.
ACE inhibitors (benazepril)	Everolimus	The risk of angioedema may be increased with concurrent administration of everolimus and benazepril.
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)	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).
Dihydropyridines (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	Digitalis glycosides	Thiazide diuretics may induce electrolyte disturbances which

Generic Name(s)	Interaction	Mechanism
(HCTZ)		may predispose patients to digitalis-induced arrhythmias.

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 13.

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

Adverse Events	Single Entity Agents	Combination Products				
	Amlodipine	Amlodipine and Benazepril	Amlodipine and Olmesartan	Amlodipine and Perindopril	Amlodipine and Valsartan	Amlodipine and Valsartan and HCTZ
Cardiovascular						
Arrhythmia	-	-	-	-	✔	-
Atrial fibrillation	-	-	-	-	1	-
Bradycardia	-	-	-	-	1	-
Cardiac murmur	-	-	-	-	✔	-
Chest pain	-	-	-	-	1	-
Edema	2 to 11	2	2 to 15	-	✔	7
Hypotension	-	-	✔	✔	✔	-
Orthostatic hypotension	-	-	✔	-	1	-
Palpitations	1 to 5	✔	1 to 5	-	✔	-
Peripheral ischemia	1	-	-	-	1	-
Peripheral edema	18 to 26	✔	18 to 26	≥2	5 to 8	-
Pitting edema	-	-	-	-	✔	-
Postural hypotension	-	-	-	-	1	-
Pulse irregularity	-	-	-	-	✔	-
Tachycardia	-	-	-	-	✔	✔
Vasculitis	1	-	-	-	1	-
Ventricular tachycardia	1	-	-	-	1	-
Central Nervous System						
Abnormal dreams	1	-	-	-	1	-
Agitation	1	-	-	-	✔	-
Amnesia	1	-	-	-	✔	-
Anxiety	-	-	-	-	3	-
Apathy	1	-	-	-	✔	-
Asthenia	-	-	✔	-	✔	-
Ataxia	-	-	-	-	✔	-
Carpal tunnel syndrome	-	-	-	-	✔	-
Cervicobrachial syndrome	-	-	-	-	✔	-
Depersonalization	1	-	-	-	1	-
Depression	-	-	-	-	✔	-
Dizziness	1	1	1 to 3	≥2	2	8
Headache	7	2	-	≥2	11	5
Hypoesthesia	-	-	-	-	✔	-
Insomnia	-	-	-	-	✔	-
Migraine	-	-	-	-	✔	-
Nervousness	1	✔	-	-	1	-
Paresthesia	-	-	-	-	✔	-
Peripheral neuropathy	1	-	-	-	1	-
Postural dizziness	-	✔	-	-	1	<1
Pyrexia	-	-	-	-	✔	-
Sciatica	-	-	-	-	✔	-
Sinus headache	-	-	-	-	✔	-
Somnolence	<2	✔	<2	-	3	✔
Syncope	-	✔	-	-	1	✔
Tremor	-	-	-	-	1	✔
Vertigo	1	-	-	-	✔	-
Dermatologic						
Alopecia	-	-	✔	-	✔	-

Adverse Events	Single Entity Agents	Combination Products				
	Amlodipine	Amlodipine and Benazepril	Amlodipine and Olmesartan	Amlodipine and Perindopril	Amlodipine and Valsartan	Amlodipine and Valsartan and HCTZ
Cold and clammy skin	1	-	-	-	✔	-
Dermatitis	-	-	-	-	✔	-
Eczema	-	-	-	-	✔	-
Erythema	-	-	-	-	✔	-
Erythema multiforme	1	-	-	-	1	-
Exanthema	-	-	-	-	✔	-
Flushing	1 to 3	✔	1 to 5	-	✔	-
Hyperhidrosis	-	-	-	-	✔	-
Pruritus	1	-	✔	-	✔	✔
Rash	1 to 2	✔	✔	✔	✔	✔
Rash, erythematous	-	-	-	-	1	-
Rash, maculopapular	✔	-	-	-	1	-
Skin discoloration	1	-	-	-	✔	-
Skin dryness	1	-	-	-	✔	-
Urticaria	1	-	✔	-	✔	-
Endocrine and Metabolic						
Gout	-	-	-	-	✔	-
Gynecomastia	✔	-	✔	-	-	-
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	-	-	-	-	✔	2
Dysphagia	1	-	-	-	1	-
Flatulence	1	-	-	-	✔	-
Gastritis	-	-	-	-	✔	✔
Gastroenteritis	-	-	-	-	✔	-
Hemorrhoids	-	-	-	-	✔	✔
Increased appetite	-	-	-	-	✔	-
Jaundice	✔	-	✔	-	-	-
Loose stools	1	-	-	-	✔	-
Nausea	3	✔	-	✔	3	2
Pancreatitis	1	-	-	-	1	-
Vomiting	-	-	✔	-	✔	-
Genitourinary						
Cystitis	-	-	-	-	✔	-
Dysuria	-	-	-	-	✔	-
Erectile dysfunction	-	-	-	-	✔	✔
Hematuria	-	-	-	-	✔	-
Impotence	-	✔	-	-	✔	-
Micturition disorder	1	-	-	-	1	-
Nephrolithiasis	-	-	-	-	✔	-
Nocturia	1	-	✔	-	1	-
Pollakiuria	-	-	-	-	✔	-
Polyuria	-	✔	-	-	✔	-
Sexual dysfunction	1	-	-	-	1	-
Urinary frequency	1	-	✔	-	✔	-
Urinary tract infection	-	-	-	-	✔	-
Hematological						
Leukopenia	-	-	-	-	1	-
Purpura	1	-	-	-	1	-
Thrombocytopenia	1	-	-	-	1	-
Laboratory Test Abnormalities						
Blood urea nitrogen increased	-	-	-	-	5 to 17	-
Creatinine increases	-	-	-	-	✔	-

Adverse Events	Single Entity Agents	Combination Products				
	Amlodipine	Amlodipine and Benazepril	Amlodipine and Olmesartan	Amlodipine and Perindopril	Amlodipine and Valsartan	Amlodipine and Valsartan and HCTZ
Hepatic enzyme elevations	✔	-	✔	-	✔	-
Hypercholesterolemia	-	-	-	-	✔	-
Hyperglycemia	1	-	-	-	1	-
Hyperkalemia	-	✔	-	2	3 to 10	-
Musculoskeletal						
Arthralgia	-	-	-	-	✔	✔
Arthrosis	1	-	-	-	1	-
Back pain	1	✔	-	-	✔	2
Hypertonia	-	-	-	-	✔	-
Joint sprain	-	-	-	-	✔	-
Joint swelling	-	-	-	-	✔	✔
Limb injury	-	-	-	-	✔	-
Malaise	1	-	-	-	1	-
Muscle cramps	1	✔	-	-	1	-
Muscle spasms	-	-	-	-	✔	2
Muscle weakness	-	-	-	-	✔	✔
Musculoskeletal chest pain	-	-	-	-	✔	-
Myalgia	1	✔	-	-	✔	-
Osteoarthritis	-	-	-	-	✔	✔
Pain	1	-	-	-	✔	-
Rhabdomyolysis	✔	-	✔	-	-	-
Twitching	1	-	-	-	✔	-
Respiratory						
Bronchitis	-	-	-	-	✔	-
Cough	-	3	-	≥2	2	✔
Dysphonia	-	-	-	-	✔	-
Dyspnea	-	-	-	-	1	-
Epistaxis	1	-	-	-	✔	-
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	-	-	-	-	✔	-
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	-	✔	-	1	-
Contusion	-	-	-	-	✔	-
Epicondylitis	-	-	-	-	✔	-
Fatigue	4.5	-	-	-	✔	2
Gingival hyperplasia	1	-	-	-	1	-
Hot flush	1	-	-	-	✔	-
Hypersensitivity	-	-	-	-	✔	-

Adverse Events	Single Entity Agents	Combination Products				
	Amlodipine	Amlodipine and Benazepril	Amlodipine and Olmesartan	Amlodipine and Perindopril	Amlodipine and Valsartan	Amlodipine and Valsartan and HCTZ
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)[1,6-17]

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	1 to 50	-
Myocardial infarction	1 to 2	≤1	≤1	✔	-	-
Orthostatic hypotension	-	-	-	-	-	1
Palpitations	<3	1 to 5	3 to 4	<7	-	3
Pedal edema	-	-	6 to 8	-	-	-
Peripheral edema	2 to 17	-	✔	7 to 10	-	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	≤1	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	-	-	-	-

Adverse Events	Felodipine	Isradipine	Nicardipine	Nifedipine	Nimodipine	Nisoldipine
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	-	-
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	-	-

Adverse Events	Felodipine	Isradipine	Nicardipine	Nifedipine	Nimodipine	Nisoldipine
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						
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 Perindopril[1]

WARNING
When pregnancy is detected, discontinue amlodipine and perindopril 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[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 12. 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 13. 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 14. Usual Dosing Regimens for the Dihydropyridines[1,2,6-17]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Amlodipine	Angina pectoris (chronic stable and vasospastic): Tablet: maintenance, 5 to 10 mg/day; maximum, 10 mg/day Coronary artery disease: Tablet: maintenance, 5 to 10 mg/day; maximum, 10 mg/day Hypertension: Tablet: initial, 5 mg/day; maintenance, 5 to 10 mg/day; maximum, 10 mg/day	Hypertension in children six to 17 years of age: 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.	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
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	Safety and efficacy in children have not been established.	Capsule: 20 mg 30 mg Injection: 25 mg/10 mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	depending on the blood pressure to be obtained and the response of the patient		
Nifedipine	Angina pectoris (chronic stable) Capsule: initial, 10 mg three times daily; maintenance, 10 to 20 mg three 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 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	Safety and efficacy in children have not been established.	Capsule: 10 mg 20 mg Extended-release tablet: 30 mg 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	Hypertension:	Safety and efficacy in	Tablet:

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
olmesartan	Tablet: initial, 5-20 mg once daily; maximum, 10-40 mg once daily	children have not been established.	5-20 mg 5-40 mg 10-20 mg 10-40 mg
Amlodipine and perindopril	Hypertension: Tablet: initial, 3.5-2.5 mg once daily; maximum, 14-10 mg once daily	Safety and efficacy in children have not been established.	Tablet: 3.5-2.5 mg 7-5 mg 14-10 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
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.[37] (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.[38] (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.[39] (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,	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			adverse events	(HR, 1.42; 95% CI, 0.88 to 2.30).
Dahlöf et al.[40] (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,	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			development of renal impairment	therapy because of a serious adverse events (2 vs 3%; P<0.0001).
Chapman et al.[41] (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	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
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				
Nissen et al.[42] (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,	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			incidence of revascularization in vessels that had undergone previous stent placement	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).
ALLHAT[43] (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	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			hospitalization, heart failure, and PAD)	(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.[44] (2008) ALLHAT Amlodipine 2.5 to 10 mg QD vs lisinopril 10 to 40 mg QD vs chlorthalidone 12.5 to 25 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).
Rahman et al.[45] (2012) ALLHAT Amlodipine 2.5 to 10 mg/day vs lisinopril 10 to 40 mg/day vs chlorthalidone	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
12.5 to 25 mg/day				
Muntner et al.[46] (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
Bangalore et al.[47] (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	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	hypertension) at 2-year follow up			
Ogihara et al.[48] (2008) CASE-J Amlodipine 2.5 to 10 mg QD vs candesartan 4 to 12 mg QD	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 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	N=4,703 Up to 4 years	Primary: First fatal or nonfatal cardiovascular event Secondary: All-cause death, new-onset diabetes, discontinuation due to adverse events	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. 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.[49] (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).

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.[50] (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).
Jamerson et al.[51] (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	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			revascularization. Secondary: Death from cardiovascular causes, nonfatal MI, and nonfatal stroke	benazepril plus HCTZ (HR, 0.79; 95% CI, 0.67 to 0.92; P=0.002).
Bakris et al.[52] (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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Weber et al.[53] (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 one 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; peripheral arterial disease, left ventricular hypertrophy; or diabetes) (Subanalysis of patients with diabetes)	N=6,946 Mean treatment duration 29.7 months for benazepril and amlodipine group and 29.5 months for benazepril and HCTZ group	Primary: Primary: Time to first event (composite of cardiovascular event and death 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	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. Peripheral edema was higher in the benazepril and amlodipine group compared to the benazepril and HCTZ group.
Weber et al.[54] (2013) ACCOMPLISH Benazepril and amlodipine 40-5 to 40-10 mg/day, followed by forced	Subanalysis of ACCOMPLISH based on body size Patients >60 years of age with HTN and at high risk of cardiovascular	N=11,482	Primary: Composite of cardiovascular death or nonfatal MI or stroke Secondary: Cardiovascular	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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)	events		death, total MI, total stroke	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; 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.[55] (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:	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Death from cardiovascular causes, nonfatal MI, and nonfatal stroke	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.
Hansson et al.[56] (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.[57] (1996)	DB, MC, positive-control, RCT	N=883	Primary: Rate of progression	Primary: There was no difference in the rate of progression of intimal-medial

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
MIDAS Isradipine 2.5 to 5 mg BID vs HCTZ 12.5 to 25 mg QD	Patients, average of 58.5 years old, with HTN	3 years	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 procedures (TIAs, dysrhythmia, aortic valve replacement, femoral popliteal bypass graft), blood pressure	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).
National Intervention Cooperative Study[58] (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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				group) and uric acid levels (increased with trichlormethiazide).
Lichtlen et al.[59] (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: Critical clinical events (cardiac death, nonfatal MI, unstable angina, need for procedure, heart failure, severe arrhythmias), progression of new lesions	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 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.[60] (2000) INSIGHT Nifedipine 30 mg QD vs amiloride and HCTZ 2.5-25 mg QD (fixed-dose combination product)	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Doses were doubled or atenolol 25 to 50 mg or enalapril 5 to 10 mg was added.				
Estacio et al.[61] (1998) ABCD Nisoldipine 10 to 60 mg/day vs enalapril 5 to 40 mg/day	DB, PRO, RCT Patients between the ages of 40 and 74 years with NIDDM, baseline DBP ≥90 mm Hg and receiving no antihypertensive medications at the time of randomization	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 the incidence and progression of complications of diabetes; compare enalapril to nisoldipine as a first-line antihypertensive agent Secondary: Incidence of MI	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 MI than enalapril (RR, 7.0; 95% CI, 2.3 to 21.4).
Hypertension				
Sheehy et al.[62] (2000) Amlodipine 2.5 to 10 mg QD vs felodipine 2.5 to	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
10 mg QD				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.[63] (1996) Amlodipine 5 to 10 mg QD vs felodipine ER 5 to 10 mg QD	DB, MC, PG, RCT Patients, age 18 to 75 years old, with mild to moderate HTN (DBP ≥95 mm Hg and ≤114 mm Hg)	N=201 12 weeks	Primary: Number of responders (DBP ≤90 mm Hg after 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	Primary: Amlodipine treatment resulted in significantly more responders than felodipine treatment (P=0.046): 68% (69 of 101) of the amlodipine group were responders. 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.[64] (2002) Amlodipine 5 mg	DB, MC, PG RCT Men and women, age 60 years and older with isolated	N=133 90 days	Primary: Mean difference in SBP from baseline to day 90	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD vs nicardipine 60 mg/day, divided 2 to 3 times daily	systolic HTN (SBP 160 to 208 mm Hg) and DBP <90 mm Hg		Secondary: Mean difference in DBP, pulse pressure, heart rate, percent of patients with normal blood pressure (<140/90 mm Hg), safety	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). 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.[65] (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.[66] (2007) i-TECHO Amlodipine 2.5 to 10 mg QD vs	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:	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
nifedipine CR 20 to 80 mg QD			Not reported	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: Not reported
Saito et al.[67] (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.[68] (2003) CESNA-II	DB, DD, PG, MC, RCT Men and women	N=not specified 6 weeks	Primary: Change from baseline in DBP at 6 weeks	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Amlodipine 5 to 10 mg QD vs nisoldipine ER 20 to 40 mg QD	with HTN (DBP 90-109 mm Hg) and CAD		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)	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.[69] (2000) Amlodipine 2.5 to 10 mg QD vs nisoldipine ER 10 to 40 mg QD	DB, DD, MC, RCT Men and women, age 21 to 75 years, with HTN	N=161 8 weeks	Primary: Between treatment comparison of change from baseline in DBP Secondary: Change from baseline in SBP, heart rate, percent of patients who responded	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 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.[70] (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	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			in clinic blood pressure and pulse	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.[71] (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 switch to nisoldipine	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: Not reported
Drummond et al.[72] (2007) Amlodipine 5 mg QD vs amlodipine 10 mg QD vs aliskiren and amlodipine 150-5 mg QD (fixed-dose combination product)	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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.				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.[73] (2000) Amlodipine 5 mg QD vs bisoprolol and HCTZ 2.5-6.25 mg QD (fixed-dose combination product)	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Prisant et al.[74] (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 enalapril 5, 10, or 20 mg	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). 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Mazza et al.[75] (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 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.[76] (2003) Amlodipine 2.5 mg/day vs eplerenone 50 mg/day Both medications were titrated to a	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
maximum of 200 (eplerenone) or 10 (amlodipine) mg/day to achieve a SBP<140 mm Hg.				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.[77] (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.	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
Jordan et al.[78] (2007) Amlodipine 5 to 10 mg QD, added to existing HCTZ	DB, DD, MC, PG, RCT Obese men and women (BMI ≥30 kg/m^2) ≥18 years	N=489 12 weeks	Primary: Change in mean sitting DBP with aliskiren 300 mg plus HCTZ vs HCTZ alone at 8	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:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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 therapy (single entity products) vs HCTZ 25 mg QD (existing therapy)	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		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 patients achieving blood pressure control (mean sitting blood pressure <140/90 mm Hg), plasma renin activity, safety and tolerability	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 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%).
Messerli et al.[79] (2002) Amlodipine and benazepril 5-10 mg to 5-20 mg QD (fixed-dose combination product)	OL Patients ≥18 years with mild-to-moderate HTN taking amlodipine 5 to 10 mg with inadequate blood pressure (DBP ≥90 mm Hg, Group 1) or intolerance with amlodipine (DBP	N=7,912 4 weeks	Primary: Change in mean sitting DBP (group 1), and percentage of patients whose edema improved (group 2) Secondary: Group 1-change in mean sitting SBP	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). 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	≤90 mm Hg with edema, Group 2)			
Chrysant et al.[80] (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 benazepril 10-20 mg/day (fixed-dose combination product) (Group 4) vs	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
amlodipine 10 mg/day (Group 5)				
Messerli et al.[81] (2000) Study 1: Amlodipine and benazepril 5-10 mg to 5-20 mg QD (fixed-dose combination product) vs nifedipine 30 to 60 mg/day Study 2: 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. 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.[82] (2004)	DB, MC, PG, RCT Men and women 18	N=364 12 weeks	Primary: Percentage of patients with SBP	Primary: Significantly more patients on combination therapy (74.2%) met the primary end point than patients on amlodipine monotherapy (53.9%;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Amlodipine and benazepril 5-20 and 10-20 mg/day (fixed-dose combination product) vs amlodipine 5 to 10 mg/day	to 80 years of age with stage 2 HTN		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	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.[83] (2005) SELECT Amlodipine and benazepril 5-20 mg/day (fixed-dose combination product) vs	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:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
amlodipine 5 mg/day vs benazepril 20 mg/day				Not reported
Kuschnir et al.[84] (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.[85] (2007) Amlodipine and benazepril 10-40 mg QD for 6 weeks (fixed-dose combination product)	DB, MC, RCT Men and women ≥18 years of age with mean sitting DBP ≥95 mm Hg not adequately controlled with amlodipine 10	N=812 6 weeks	Primary: Reduction in mean sitting DBP and SBP, reductions in ambulatory blood pressure, successful response (mean sitting DBP <90	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 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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	mg/day monotherapy		mm Hg or decrease of ≥10 mm Hg from baseline), safety Secondary: Not reported	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.[86] (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 QD for 8 weeks	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). Secondary: Not reported
Fogari et al.[87] (1997)	DB, MC, PC, RCT	N=448	Primary: Reduction in mean	Primary: Significantly greater reductions in sitting DBP were observed with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Amlodipine and benazepril 2.5-10 to 5-10 mg QD (fixed-dose combination product) vs benazepril 10 mg QD	Men and women 24 to 73 years of age (mean 55 years) with HTN inadequately controlled with ACE inhibitor monotherapy	8 weeks	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)	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.[88] (2007) Losartan 50 mg/day and HCTZ 12.5 mg/day vs candesartan 8 mg QD or amlodipine 5 mg QD	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. 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Hilleman et al.[89] (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.[90] (2007) ACCOMPLISH Amlodipine 5 mg QD plus benazepril 20 mg QD vs benazepril 20 mg QD plus HCTZ	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)	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
12.5 mg QD			Secondary: Not reported	Secondary: Not reported
Malacco et al.[91] (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.[92] (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	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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				
Tatti et al.[93] (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). No difference in fibrinogen levels was observed between the groups at the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				end of the trial (P>0.05).
Miranda et al.[94](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.[95] (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.[96] (2007)	DB, DD, RCT	N=194	Primary: Difference	Primary: After 12 weeks, mean reductions in SBP were significantly larger in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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	between treatment groups in mean change in ABPM for last 9 hours of treatment and during drug holiday Secondary: Not reported	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.[97] (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.[98] (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.[99] (2009)	OL, ES	N=1,684	Primary: Reduction in mean	Primary: Mean sitting DBP decreased from 101.5 mm Hg at baseline to 81.9 mm

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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)	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)	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.[100] (2009) COACH	DB, factorial, MC, PC, RCT Patients ≥18 years	N=1,940 8 weeks	Primary: Mean change in DBP and SBP at week 8 for each	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

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	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		subgroup Secondary: Proportion of patients achieving blood pressure goal (<140/90 mm Hg or <130/80 mm Hg)	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.[101] (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.
Elliott et al.[102]	PRO, RCT	N=820	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2015) Amlodipine 10 mg QD vs perindopril 16 mg QD vs perindopril + amlodipine 14-10 mg QD	Hypertensive patients 18 to 75 years of age	42 days	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	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.[103] (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.[104] (2009) Amlodipine 2.5 to	DB, MC, PC, RCT Patients ≥18 years of age with Stage 1	N=2,607 8 weeks	Primary: Change in the in-clinic seated diastolic BP	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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	or 2 HTN (DBP ≥95 and ≤119 mm Hg)		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)	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.[105] (2009) Telmisartan and amlodipine 40-5 mg QD (fixed-dose combination product) vs telmisartan and amlodipine 40-10 mg QD (fixed-	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 response (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). Combination therapy resulted in a greater DBP and SBP response than

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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			<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	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.[106] (2007) Telmisartan and amlodipine 40-5 mg QD (fixed-dose combination) vs amlodipine	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; amlodipine, from 99.7 to 94.3 mm Hg; both, P<0.05). There was a 20.2%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
5 mg QD				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.[107] (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%).
Maciejewski et	DB, PRO, RCT, XO	N=20	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
al.[108] (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.	African-Americans, older than 35 years, with baseline blood pressure >140/90 mm Hg and not on antihypertensive treatment	8 to 10 weeks for each arm with 2 week washout period before crossover	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	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.[109] (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.[110] (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.[111] (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.[112] (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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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.[113] (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.[114] (2009) Amlodipine and valsartan 10-160	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).

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mg 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.[115] (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.[116] (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.[117] (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.[118] (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	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	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
valsartan 5-160 mg QD for 4 weeks (fixed-dose combination product)			patients and <130/80 mm Hg for diabetic patients), and SBP response (mean sitting SBP <130 mm Hg or ≥20 mm Hg reduction from baseline)	10 mg to amlodipine and valsartan at week 12 (38.04 vs 31.81%; P=0.162). 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.[119] (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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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.
Fogari et al.[120] (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.[121] (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

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				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).
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	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
combination product)				
Calhoun et al.[123] (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.[124] (2010)	AC, MC, OL, RCT	N=190	Primary: Change in SBP and	Primary: At the end of four weeks, the mean change in SBP (-30.0±10.4 vs -

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Amlodipine 2.5 to 5 mg and atenolol 25 to 50 mg QD vs atenolol 25 to 50 mg QD	Adults with either untreated or pretreated essential HTN	12 weeks	DBP Secondary: Not reported	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
Gustin et al.[125] (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.[126] (2006) Felodipine 5 mg QD vs lisinopril 10 mg QD vs chlorthalidone 12.5	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	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
mg QD vs valsartan 80 mg QD All patients also received diltiazem 240 mg QD.	weeks of OL monotherapy with diltiazem at 240 mg QD			
Manyemba et al.[127] (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.[128] (2005) Other antihypertensive therapies (amiloride, amlodipine, bendro-flumethiazide*, captopril, diltiazem, enalapril, felodipine, HCTZ,	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:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
isradipine, lacidipine, lisinopril, losartan, or verapamil) or placebo vs β-blocker therapy (atenolol, metoprolol, oxprenolol*, pindolol, or propranolol)				Not reported
Van Bortel et al.[129] (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;

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
Wiysonge et al.[130] (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

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.
Baguet et al.[131] (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.	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
Although cicletanine*, furosemide and spironolactone were considered for inclusion, none of the trials relating to these agents satisfied all inclusion criteria.				Secondary: Not reported
Renal Effects				
Esnault et al.[132] (2008) Amlodipine 5 to 10 mg QD vs enalapril 5 to 20 mg/day	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.
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	DB, MC, RCT Patients were self-identified African Americans aged 18	N=1,094 3 to 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
10 mg/day vs metoprolol 50 to 200 mg/day vs ramipril 2.5 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.
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)	AC, DB, RCT	N=332	Primary: Change in UAER;	Primary: Valsartan resulted in a UAER reduction of 44% at 24 weeks compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
MARVAL Amlodipine 5 mg QD vs valsartan 80 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.	Patients 35 to 75 years old with type 2 diabetes mellitus and microalbuminuria, with or without HTN	24 weeks	proportion of patients who returned to normal albuminuria Secondary: Proportion of patients returning to normoalbuminuria	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).
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:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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) 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				

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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.
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)	RCT Patients with aneurismal	N=104 7 days	Primary: Incidence of clinical vasospasm and transcranial	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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	subarachnoid hemorrhage		Doppler angiographic vasospasm, and infarction attributable to vasospasm Secondary: Incidence of angiographic vasospasm	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).
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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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, 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).[71] 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.[62]

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	tablet	Norvasc®*	$$	$
Felodipine	extended-release tablet	N/A	N/A	$
Isradipine	capsule*, extended-release tablet	N/A	N/A	$$$$$
Nicardipine	capsule, injection, sustained-release capsule	N/A	N/A	$$
Nifedipine	capsule, extended-release tablet	Adalat CC®*, Procardia®*, Procardia XL®*	$$$	$$
Nimodipine	capsule, solution	Nymalize®	$$$$$	$$$
Nisoldipine	extended-release tablet*	Sular ER®*	N/A	$$$$$
Combination Products				
Amlodipine and benazepril	capsule	Lotrel®*	$$$$	$
Amlodipine and olmesartan	tablet	Azor®*	$$$$$	$$
Amlodipine and perindopril	tablet	Prestalia®	$$$$	N/A
Amlodipine and valsartan	tablet	Exforge®*	$$$$$	$$
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.[1,2,6-17] Amlodipine is available in combination with benazepril, olmesartan, perindopril, 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 and amlodipine- perindopril are available in a generic formulation.

There are several national and international guidelines that provide recommendations regarding the use of calcium-channel blocking agents.[18-36] 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.[18-24] Calcium-channel blocking agents are recommended as initial therapy in patients

with variant/vasospastic angina.[19,22] 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; however, amlodipine or felodipine may be added if patients have angina or uncontrolled blood pressure.[26-28] There are several published guidelines on the treatment of hypertension. Thiazide-type diuretics are frequently recommended as initial therapy in patients with uncomplicated hypertension.[29-35] 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.[29-35] Most patients will require more than one antihypertensive medication to achieve blood pressure goals.[29-35]

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.[62-131] Most patients will require more than one antihypertensive agent to achieve blood pressure goals.[29-35] The use of a fixed-dose combination product may simplify the treatment regimen and improve adherence.[31,32,143-145] 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.[39-61]

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.[1-5]

The miscellaneous calcium-channel blocking agents include diltiazem and verapamil, which are approved for the treatment of angina, arrhythmias, and hypertension.[1,2,6-14] 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. [1,2,6-14] Verapamil dilates coronary and peripheral arteries. It also slows conduction through the AV node, and has negative inotropic and chronotropic effects. [1,2,6-14] 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 a generic formulation. This class was last reviewed in August 2015.

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®*, 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 College of Cardiology/ American Heart Association: **2007 Chronic Angina Focused Update of the 2002 Guidelines for the**	• Aspirin should be started at 75 to 162 mg/day and continued indefinitely in all patients, unless contraindicated. • Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with an increased risk of bleeding and should be monitored closely. • Patients with hypertension and established coronary artery disease (CAD) should be treated with blood pressure medication(s) as tolerated, including angiotensin converting enzyme (ACE) inhibitors and/or β-adrenergic antagonists (β-blockers) with the addition of other medications as needed to achieve blood pressure goals of

Clinical Guideline	Recommendations
Management of Patients With Chronic Stable Angina (2007)[15]	<140/90 or <130/80 mm Hg for patients with chronic kidney disease or diabetes. • Long-acting calcium channel blocking agents or long-acting nitrates may be used if β-blockers are contraindicated. Immediate-release and short-acting dihydropyridine calcium channel blockers can increase adverse cardiac events and should not be used. • Long-acting calcium channel blockers or long-acting nitrates may be used with β-blockers if initial treatment is not successful. • ACE inhibitors should be used indefinitely in patients with a left ventricular ejection fraction (LVEF) ≤40% and in those with hypertension, diabetes or chronic kidney disease, unless contraindicated. • ACE inhibitors should also be used indefinitely in patients at lower risk (mildly reduced or normal LVEF in whom cardiovascular risk factors remain well controlled and revascularization has been performed), unless contraindicated. • Angiotensin II receptor blockers (ARBs) are recommended in patients with hypertension, those who have an indication for an ACE inhibitor and are intolerant to them, who have heart failure, or who have had a myocardial infarction (MI) and have a LVEF ≤40%. • ARBs may be considered in combination with an ACE inhibitor for heart failure due to left ventricular systolic dysfunction. • Aldosterone blockade is recommended in patients post-MI without significant renal dysfunction or hyperkalemia who are already receiving therapeutic doses of an ACE inhibitor and a β-blocker, have a LVEF ≤40% and have either diabetes or heart failure. • It is beneficial to start and continue β-blocker therapy indefinitely in all patients who have had a MI, acute coronary syndrome or left ventricular dysfunction with or without heart failure symptoms, unless contraindicated. • Annual influenza vaccination is recommended in patients with cardiovascular disease.
European Society of Cardiology: **Guidelines on the Management of Stable Coronary Artery Disease (2013)[16]**	<u>General management of stable coronary artery disease (SCAD) patients</u> • The goal of management of SCAD is to reduce symptoms and improve prognosis. • The management of CAD patients encompasses lifestyle modification, control of CAD risk factors, evidence-based pharmacological therapy, and patient education. <u>General considerations for pharmacological treatments in SCAD patients</u> • 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. <u>Pharmacological treatments for angina/ischemia relief in SCAD patients</u> • Short-acting nitrates are recommended. • First-line treatment is indicated with ß-blockers and/or calcium channel blockers to control heart rate and symptoms. • For second-line treatment it is recommended to add long-acting nitrates or ivabradine or nicorandil* or ranolazine, according to heart rate, blood pressure, and tolerance. • For second-line treatment, trimetazidine* may be considered. • 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 β-blockers avoided.

Clinical Guideline	Recommendations
	Pharmacological treatments for event prevention in SCAD patients • Low-dose aspirin daily is recommended in all SCAD patients. • Clopidogrel is indicated as an alternative in case of aspirin intolerance. • Statins are recommended in all SCAD patients. • It is recommended to use ACE inhibitors (or ARBs) if presence of other conditions (e.g. heart failure, hypertension or diabetes). Treatment in patients with microvascular angina • It is recommended that all patients receive secondary prevention medications including aspirin and statins. • β-blockers are recommended as a first line treatment. • Calcium antagonists are recommended if β-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 (aminophylline, bamiphylline*) or non-pharmacological treatments such as neurostimulatory techniques may be considered in patients with symptoms refractory to the above listed drugs.
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)**[17]	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**	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

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of Cardiology Foundation Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes (2014)[18]	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 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-

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	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 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

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	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 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.

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	• Late hospital and post-hospital oral antiplatelet therapy
	  ○ 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.
	  ○ 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.
	  ○ 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
	  ○ 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.
	  ○ 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: **Guideline for the Management of Acute Coronary Syndromes in Patients Presenting Without Persistent ST-Segment Elevation (2015)[19]**	Pharmacological treatment of ischemia
	• Early initiation of β-blocker treatment is recommended in patients with ongoing ischemic symptoms and without contraindications.
	• 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.
	
	Recommendations for platelet inhibition in non-ST-elevation acute coronary syndromes
	• 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.
	  ○ 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.
	• 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.
	
	Recommendations for anticoagulation in non-ST-elevation acute coronary syndromes

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	• 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 CHADS2-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. • 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 CHADS2-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

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	anticoagulant should be considered for up to one year.
American College of Cardiology/ American Heart Association: **Guideline for the Management of ST-Elevation Myocardial Infarction (2013)**[20]	Routine medical therapies: calcium channel blockers • 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. Routine medical therapies: β-blockers • 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. Routine medical therapies: Renin-Angiotensin-Aldosterone System Inhibitors • 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. 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 (2012)**[21]	Routine therapies in the acute, subacute and long term phase of STEMI • Active smokers with STEMI must receive counseling and be referred to a smoking cessation program. • Each hospital participating in the care of STEMI patients must have a smoking cessation protocol. • Exercise-based rehabilitation is recommended. • Antiplatelet therapy with low dose aspirin (75 to 100 mg) is indicated indefinitely after STEMI. • In patients intolerant to aspirin, clopidogrel is indicated as an alternative. • Dual antiplatelet therapy with a combination of aspirin and prasugrel or aspirin and ticagrelor is recommended (over aspirin and clopidogrel) in patients treated with PCI. • Dual antiplatelet therapy with aspirin and an oral ADP receptor antagonist must be continued for up to 12 months after STEMI, with a strict minimum of 1 month for

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	patients receiving bare metal stent and 6 months for patients receiving drug-eluting stent. • In patients with left ventricular thrombus, anticoagulation should be instituted for a minimum of 3 months. • In patients with a clear indication for oral anticoagulation (e.g. atrial fibrillation with CHA2DS2-VASc Score ≥2 or mechanical valve prosthesis), oral anticoagulation must be implemented in addition to antiplatelet therapy. • If patients require triple antithrombotic therapy, combining dual antiplatelet therapy and oral anticoagulant, e.g. because of stent placement and an obligatory indication for oral anticoagulation, the duration of dual antiplatelet therapy should be minimized to reduce bleeding risk. • 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 1 year in patients with STEMI who did not receive a stent. • Gastric protection with a proton pump inhibitor should be considered for the duration of DAPT therapy in patients at high risk of bleeding. • 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. • Intravenous β-blockers must be avoided in patients with hypotension or heart failure. • Intravenous β-blockers should be considered at the time of presentation in patients 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. • Reassessment of LDL-cholesterol should be considered after 4–6 weeks to ensure that a target value of ≤70 mg/dL has been reached. • Verapamil may be considered for secondary prevention in patients with absolute contraindications to β-blockers and no heart failure. • 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.

National Institute for Health and Clinical Excellence: **Myocardial Infarction: cardiac rehabilitation and prevention of further cardiovascular**	Drug therapy
	• Offer all people who have had an acute MI treatment with the following drugs:
	  ○ ACE inhibitor
	  ○ Dual antiplatelet therapy (aspirin plus a second antiplatelet agent)
	  ○ β-blocker
	  ○ Statin
	
	Antiplatelet therapy
	• Offer aspirin to all people after an MI and continue indefinitely, unless they are

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disease (2013)[22]	aspirin intolerant or have an indication for anticoagulation. • Offer aspirin to people who have had an MI more than 12 months ago and continue it indefinitely. • For patients with aspirin hypersensitivity, clopidogrel monotherapy should be considered as an alternative treatment. • Special considerations should be made for people with dyspepsia. • After appropriate treatment, people with a history of aspirin-induced ulcer bleeding whose ulcers have healed and who are negative for Helicobacter pylori should be considered for treatment in line with dyspepsia. • Ticagrelor in combination with low-dose aspirin is recommended for up to 12 months as a treatment option in adults with ACS (STEMI, PCI, or NSTEMI). • Offer clopidogrel as a treatment option for up to 12 months to people who have had an NSTEMI, regardless of treatment, or people who have had a STEMI and received a bare-metal or drug-eluting stent. • Offer clopidogrel as a treatment option for at least one month and consider continuing for up to 12 months in people who have had a STEMI and medical management with or without reperfusion treatment with a fibrinolytic agent. • Continue the second antiplatelet agent for up to 12 months in people who have had a STEMI and who received CABG surgery. • Offer clopidogrel instead of aspirin to people who also have other clinical vascular disease (had an MI and stopped dual antiplatelet therapy or had an MI more than 12 months ago). <u>Antiplatelet therapy in people with an indication for anticoagulation</u> • Take bleeding risk, thromboembolic risk, and cardiovascular risk into account when deciding which people who have had an MI and have an indication for anticoagulation. • Unless there is a high risk of bleeding, continue anticoagulation and add aspirin to treatment in people who have had an MI who otherwise need anticoagulation and who have had their condition managed medically or have undergone balloon angioplasty or have undergone CABG surgery. • Continue anticoagulation and add clopidogrel to treatment in people who have had an MI, who have undergone PCI with bare-metal or drug-eluting stents and who otherwise need anticoagulation. • Offer clopidogrel with warfarin to people with a sensitivity to aspirin who otherwise need anticoagulation and aspirin and who have had an MI. • Do not routinely offer warfarin in combination with prasugrel or ticagrelor to people who need anticoagulation who have had an MI. • After 12 months since the MI, continue anticoagulation and take into consideration the need for ongoing antiplatelet therapy, taking into account all of the following: indication for anticoagulation, thromboembolic risk, bleeding risk, cardiovascular risk and the person's wishes. • Do not add a new oral anticoagulant (rivaroxaban, apixaban or dabigatran) in combination with dual antiplatelet therapy in people who otherwise need anticoagulation, who have had an MI. • Consider using warfarin and discontinuing treatment with a new oral anticoagulant (rivaroxaban, apixaban, or dabigatran) in people who otherwise need anticoagulation and who have had an MI, unless there is a specific clinical indication to continue it.
American College of Cardiology/ American Heart Association: **Guideline for the Management of**	<u>Treatment of Stage A heart failure (HF)</u> • Hypertension and lipid disorders should be controlled in accordance with guidelines to lower the risk of HF. (Level of Evidence (LoE): A) • Other conditions that may lead to or contribute to HF, such as obesity, diabetes mellitus, tobacco use, and known cardiotoxic agents, should be controlled or avoided. (LoE: C)

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Heart Failure (2013)[23]	<u>Treatment of Stage B heart failure</u> • In patients with a history of MI and reduced EF, ACE inhibitors or ARBs should be used to prevent HF. (LoE: A) • In patients with MI and reduced EF, evidence-based β-blockers (using one of three proven to reduce mortality [i.e., bisoprolol, carvedilol, and sustained-release metoprolol succinate]) should be used to prevent HF. (LoE: B) • In patients with MI, statins should be used to prevent HF. (LoE: A) • ACE inhibitors and β-blockers should be used in all patients with a reduced EF to prevent symptomatic HF, even if they do not have a history of MI. (LoE: A and C, respectively) • Blood pressure should be controlled to prevent symptomatic HF. (LoE: A) • Nondihydropyridine calcium channel blockers may be harmful in patients with low LVEF. (LoE: C) <u>Pharmacological treatment for Stage C HFrEF</u> • Recommendations for patients in Stages A and B are recommended where appropriate for patients in Stage C. (LoE: A, B, and C as appropriate) • Diuretics are recommended in patients with HFrEF who have evidence of fluid retention, unless contraindicated, to improve symptoms. (LoE: C) • ACE inhibitors are recommended in patients with HFrEF and current or prior symptoms, unless contraindicated, to reduce morbidity and mortality. ARBs are recommended as alternative therapy in ACE inhibitor intolerant patients. (LoE: A) • Use of one of the three β-blockers proven to reduce mortality is recommended for all patients with current or prior symptoms of HFrEF, unless contraindicated, to reduce morbidity and mortality. (LoE: A) • Aldosterone receptor antagonists are recommended in patients with NYHA class II–IV HF and who have LVEF of ≤35%, unless contraindicated, to reduce morbidity and mortality. Patients with NYHA class II HF should have a history of prior cardiovascular hospitalization or elevated plasma natriuretic peptide levels to be considered for aldosterone receptor antagonists. Creatinine should be ≤2.5 mg/dL in men or ≤2.0 mg/dL in women (or estimated glomerular filtration rate >30 mL/min/1.73 m^2), and potassium should be <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) • The combination of hydralazine and isosorbide dinitrate is recommended to reduce morbidity and mortality for patients self-described as African Americans with NYHA class III–IV HFrEF receiving optimal therapy with ACE inhibitors and β-blockers, unless contraindicated. (LoE: A) • Digoxin can be beneficial in patients with HFrEF, unless contraindicated, to decrease hospitalizations for HF. (LoE: B) • Patients with chronic HF with permanent/persistent/paroxysmal AF and an additional risk factor for cardioembolic stroke (history of hypertension, diabetes mellitus, previous stroke or transient ischemic attack, or ≥75 years of age) should receive chronic anticoagulant therapy. (LoE: A) • Statins are not beneficial as adjunctive therapy when prescribed solely for the diagnosis of HF in the absence of other indications for their use. (LoE: A) • Calcium channel blockers are not recommended as routine treatment for patients with HFrEF. (LoE: A) <u>Pharmacological treatment for Stage C HFpEF</u> • Blood pressure should be controlled according to published clinical practice guidelines. (LoE: B) • Diuretics should be used for relief of symptoms due to volume overload. (LoE: C)

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	• The use of β-blocking agents, ACE inhibitors, and ARBs in patients with hypertension is reasonable to control blood pressure in patients with HFpEF. (LoE: C) <u>Treatment of Stage D (advanced/refractory) HF</u> • Fluid restriction (1.5 to 2 L/d) is reasonable, especially in patients with hyponatremia, to reduce congestive symptoms. (LoE: C) • Until definitive therapy (e.g., coronary revascularization, mechanical circulatory support, heart transplantation) or resolution of the acute precipitating problem, patients with cardiogenic shock should receive temporary intravenous inotropic support to maintain systemic perfusion and preserve end-organ performance. (LoE: C) • Continuous intravenous inotropic support is reasonable as "bridge therapy" in patients with stage D HF refractory to medical therapy and device therapy who are eligible for and awaiting mechanical circulatory support or cardiac transplantation. (LoE: B) • Long-term use of either continuous or intermittent, intravenous parenteral positive inotropic agents, in the absence of specific indications or for reasons other than palliative care, is potentially harmful in the patient with HF. (LoE: B)
Heart Failure Society of America: **Heart Failure Society of America 2010 Comprehensive Heart Failure Practice Guidelines (Executive Summary) (2010)[24]**	<u>Patients with left ventricular systolic dysfunction</u> • ACE inhibitors should be used in all patients with a LVEF ≤40%, unless otherwise contraindicated. • ARBs may be used in patients who are intolerant to ACE inhibitors. Hydralazine and a nitrate may be used in patients intolerant to ACE inhibitors and ARBs, or in whom such therapy is contraindicated. • The combination of an ACE inhibitor and a β-blocker is recommended in all patients with a LVEF ≤40%. • The routine use of an ARB with a combination of an ACE inhibitor and β-blocker in patients who have had a MI and have left ventricular dysfunction is not recommended. • The addition of an ARB can be considered in patients with heart failure due to reduced LVEF who have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor and a β-blocker. • Individual ARBs may be considered as initial therapy (instead of an ACE inhibitor) in patients with heart failure who have had a MI and in patients with chronic heart failure and systolic dysfunction. • ARBs are recommended in patients who cannot tolerate ACE inhibitors due to cough. The combination of hydralazine and an oral nitrate may be considered in such patients not tolerating ARB therapy. • Patients intolerant to ACE inhibitors from hyperkalemia or renal insufficiency are likely to experience the same side effects with ARBs. In these cases, the combination of hydralazine and an oral nitrate should be considered. • ARBs should be considered in patients experiencing angioedema while on ACE inhibitors based on their underlying risk and with recognition that angioedema has been reported infrequently with ARBs. The combination of hydralazine and oral nitrates may be considered in such patients not tolerating ARB therapy. • A combination of hydralazine and an oral nitrate is recommended in African American patients with heart failure and reduced left ventricular ejection fraction (LVEF) who are on a standard regimen of an ACE inhibitor (or ARB) and a β-blocker. • A combination of hydralazine and an oral nitrate may be considered in non–African American patients with heart failure and reduced LVEF who are symptomatic despite optimization of standard therapy. • Administration of an aldosterone antagonist is recommended for patients with New York Heart Association (NYHA) class IV (or class III, previously class IV) heart

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	failure from reduced LVEF (<35%) while receiving standard therapy, including diuretics. • Administration of an aldosterone antagonist should be considered in patients following an acute MI, with clinical heart failure signs and symptoms or history of diabetes mellitus, and an LVEF <40%. Patients should be on standard therapy, including an ACE inhibitor (or ARB) and a β-blocker. • The triple combination of an ACE inhibitor, an ARB, and an aldosterone antagonist is not recommended because of the high risk of hyperkalemia. <u>Patients with hypertension and symptomatic left ventricular dysfunction with left ventricular dilation and low LVEF</u> • ACE inhibitors, ARBs, β-blockers, aldosterone inhibitors, and isosorbide dinitrate/hydralazine in various combinations (with a loop diuretic if needed) are recommended. • If blood pressure remains >130/80 mm Hg, a dihydropyridine calcium channel blocker (e.g., amlodipine or felodipine) may be considered or other antihypertensive medication doses increased. <u>Managing heart failure in special populations</u> • The combination of hydralazine/isosorbide dinitrate is recommended for African American women with moderate to severe heart failure symptoms who are on background neurohormonal inhibition. • A combination of hydralazine and isosorbide dinitrate is recommended as part of standard therapy in addition to β-blockers and ACE-inhibitors for African Americans with left ventricular systolic dysfunction and NYHA class II-IV heart failure. • As in all patients, but especially in the elderly, careful attention to volume status, the possibility of symptomatic cerebrovascular disease and the presence of postural hypotension are recommended during therapy with ACE inhibitors, β-blockers and diuretics. <u>Patients with heart failure and preserved LVEF</u> • ACE inhibitors or ARBs should be considered in this patient population. • ACE inhibitors should be considered in patients with heart failure and symptomatic atherosclerotic cardiovascular disease or diabetes and at least one other risk factor. ARBs may be used in patients who are intolerant to ACE inhibitors. • Beta-blocker treatment is recommended in patients with HF and preserved LVEF who have prior MI, hypertension, or AF. • Calcium channel blockers should be considered in patients with heart failure and preserved LVEF who have atrial fibrillation requiring ventricular rate control and intolerance to β-blockers (consider diltiazem or verapamil), symptom-limiting angina, or hypertension. • Diuretic therapy is recommended in all patients with heart failure and clinical evidence of volume overload, including those with preserved LVEF. • Treatment may begin with either a thiazide or loop diuretic. In more severe volume overload or if response to a thiazide is inadequate, treatment with a loop diuretic should be implemented. • Excessive diuresis, which may lead to orthostatic changes in blood pressure and worsening renal function, should be avoided. <u>Patients with heart failure and CAD</u> • Calcium channel blockers should be considered in patients who have angina despite optimization of β-blocker and nitrates. Amlodipine and felodipine are preferred in patients with decreased systolic function.

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	Patients with heart failure and hypertension • Patients with left ventricular hypertrophy or left ventricular dysfunction without left ventricular dilation should be treated to a goal blood pressure of <130/80 mm Hg. Treatment with several drugs may be necessary, including an ACE inhibitor (or ARB), a diuretic and a β-blocker or calcium channel blocker. • Patients with asymptomatic left ventricular dysfunction and left ventricular dilation and a reduced ejection fraction should receive an ACE inhibitor and a β-blocker. If blood pressure remains elevated (>130/80 mm Hg), the addition of a diuretic is recommended, followed by a calcium channel blocker or other antihypertensive agent. • If blood pressure remains >130/80 mm Hg, then the addition of a thiazide diuretic is recommended, followed by a dihydropyridine calcium channel blocker (e.g., amlodipine or felodipine) or other antihypertensive drugs. Patients at risk for development of heart failure • ACE inhibitors are recommended in patients who are at risk for the development of heart failure including patients with CAD, peripheral vascular disease, stroke, diabetes and another major risk factor, and patients with diabetes who smoke and have microalbuminuria. Patients with asymptomatic heart failure and reduced LVEF • ACE inhibitors are recommended in asymptomatic patients with reduced LVEF (<40%). • ARBs may be used in patients who are intolerant to ACE inhibitors. • Routine use of a combination of ACE inhibitors and ARBs is not recommended. • β-blocker therapy should be considered. Patients with heart failure and ischemic heart disease • ACE inhibitor therapy is recommended in all patients with either reduced or preserved LVEF after a MI. • Beta-blockers are recommended for the management of all patients with reduced LVEF or post-MI. • ACE inhibitor and β-blocker therapy should be initiated early (<48 hours) during hospitalization in hemodynamically stable patients who are post-MI with reduced LVEF or heart failure. • Calcium channel blockers may be considered in patients with HF who have angina despite the optimal use of β-blockers and nitrates. Managing heart failure in the elderly, women and African Americans • Standard regimens of ACE inhibitors and β-blockers are recommended in elderly patients with heart failure. • ACE inhibitor and β-blocker therapy are recommended in all women with heart failure and left ventricular systolic dysfunction. • ACE inhibitor and β-blocker therapy are recommended in all African American patients with heart failure and left ventricular systolic dysfunction. ARBs may be substituted in patients who are intolerant to ACE inhibitors. Heart failure in patients with reduced ejection fraction • ACE inhibitors are recommended in asymptomatic patients with reduced LVEF (<40%). • ARBs may be used in patients who are intolerant to ACE inhibitors. • β-blockers shown to be effective in clinical trials of patients with heart failure are recommended for patients with a LVEF ≤40%. • The combination of a β-blocker and an ACE inhibitor is recommended as routine therapy for asymptomatic patients with a LVEF ≤40%. The evidence is stronger in

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	patients with a history of MI. • β-blocker therapy is recommended for patients with a recent decompensation of heart failure after optimization of volume status and successful discontinuation of intravenous diuretics and vasoactive drugs. Whenever possible, β-blocker therapy should be initiated in the hospital setting at a low dose prior to discharge of stable patients. • β-blocker therapy is recommended in the great majority of patients with heart failure and reduced LVEF, even if there is concurrent diabetes, chronic obstructive pulmonary disease or peripheral vascular disease. Caution may be warranted in these patients. • It is recommended that β blockade be initiated at low doses and uptitrated gradually. • It is recommended that β-blocker therapy be continued in most patients experiencing a symptomatic exacerbation of heart failure during chronic maintenance treatment, unless they develop cardiogenic shock, refractory volume overload or symptomatic bradycardia. • The routine use of an ARB is not recommended in addition to an ACE inhibitor and a β-blocker in patients with a recent acute MI and reduced LVEF. • The addition of an ARB should be considered in patients with heart failure due to reduced LVEF who have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor and a β-blocker. • Administration of an aldosterone antagonist is recommended for patients with NYHA class IV (or class III, previously class IV) HF from reduced LVEF (<35%) while receiving standard therapy, including diuretics. • Diuretic therapy is recommended to restore and maintain normal volume status in patients with clinical evidence of fluid overload, generally manifested by congestive symptoms or signs of elevated filling pressures. Loop diuretics rather than thiazide-type diuretics are typically necessary to restore normal volume status in patients with heart failure. • The initial dose of diuretic may be increased as necessary to relieve congestion, and restoration of normal volume status may require multiple adjustments, especially in patients with severe fluid overload evidenced by massive edema or ascites. After a diuretic effect is achieved with loop diuretics (short acting), increasing administration frequency to twice or even three times/day will provide more diuresis with less physiologic perturbation than larger single doses. • Oral torsemide may be considered in patients in whom poor absorption of oral medication or erratic diuretic effect may be present. Particularly in patients with right-sided heart failure and refractory fluid retention despite high doses of other loop diuretics. • Intravenous administration of diuretics may be necessary to relieve congestion. • Diuretic refractoriness may represent patient nonadherence, a direct effect of diuretic use on the kidney or progression of underlying cardiac dysfunction. • Addition of chlorothiazide or metolazone, once or twice daily, to loop diuretics should be considered in patients with persistent fluid retention despite high dose loop diuretic therapy. Chronic daily use should be avoided if possible because of the potential for electrolyte shifts and volume depletion. These drugs may be used periodically (every other day or weekly) to optimize fluid management. Metolazone will generally be more potent and much longer acting in this setting and in patients with chronic renal insufficiency, so administration should be adjusted accordingly. Volume status and electrolytes must be monitored closely when multiple diuretics are used. • Careful observation for the development of side effects is recommended in patients treated with diuretics, especially when high doses or combination therapy are used. Patients should undergo routine laboratory studies and clinical examination as dictated by their clinical response.

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	• Patients requiring diuretic therapy to treated fluid retention associated with heart failure generally require chronic treatment, although often at lower doses than those required initially to achieve diuresis. Decreasing or discontinuing therapy may be considered in patients experiencing significant improvement in clinical status and cardiac function or in those who successfully restrict dietary sodium intake. These patients may undergo cautious weaning of diuretic dose and frequency with careful observation for recurrent fluid retention.
	• Patients and caregivers should be given education on the early signs of fluid retention and the plan for initial therapy.
	• Selected patients may be educated to adjust daily dose of diuretic in response to weight gain from fluid overload.
	
	<u>Evaluation and management of patients with acute decompensated heart failure</u>
	• Patients admitted with acute decompensated heart failure and evidence of fluid overload be treated initially with loop diuretics; usually given intravenously rather than orally. Ultrafiltration may be considered in lieu of diuretics.
	• Diuretics should be administered at doses needed to produce a rate of diuresis sufficient to achieve optimal volume status with relief of signs and symptoms of congestion, without inducing an excessively rapid reduction in intravascular volume or serum electrolytes.
	• Monitoring of daily weights, intake and output is recommended to assess clinical efficacy of diuretic therapy.
	• Careful observation for development of a variety of side effects, including renal dysfunction, electrolyte abnormalities, symptomatic hypotension and gout is recommended in patients treated with diuretics, especially when high doses or combination therapy is used.
	• Careful observation for the development of renal dysfunction is recommended in patients treated with diuretics. Patients with moderate to severe renal dysfunction and evidence of fluid retention should continue to be treated with diuretics. In the presence of severe fluid overload, renal dysfunction may improve with diuresis.
	• When congestion fails to improve in response to diuretic therapy, the following options should be considered:
	  ○ Re-evaluating the presence/absence of congestion.
	  ○ Sodium and fluid restriction.
	  ○ Increasing doses of loop diuretic.
	  ○ Continuous infusion of a loop diuretic.
	  ○ Addition of a second type of diuretic orally (metolazone or spironolactone) or intravenously (chlorothiazide).
	  ○ Ultrafiltration may be considered as well.

European Society of Cardiology: **Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (2016)**[25]	<u>Pharmacological treatments indicated in patients with symptomatic (NYHA Class II-IV) heart failure with reduced ejection fraction</u> • An ACE inhibitor is recommended, in addition to a beat-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death. • A mineralocorticoid receptor antagonist 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. • Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion. • 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. • 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

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	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. • 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 heart failure with preserved ejection fraction and heart failure with mid-range ejection fraction</u> • It is recommended to screen patients with HFpEF or HFmrEF (mid-range) 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 or HFmrEF in order to alleviate symptoms and signs. <u>Recommendations for initial management of a rapid ventricular rate in patients with heart failure and atrial fibrillation in the acute or chronic setting</u> • Urgent electrical cardioversion is recommended if AF is thought to be contributing to the patient's hemodynamic compromise in order to improve the patient clinical condition. • For patients in NYHA Class IV, in addition to treatment for acute HF, an intravenous bolus of amiodarone or, in digoxin-naïve patients, an intravenous bolus of digoxin should be considered to reduce the ventricular rate. • For patients in NYHA Class I–III, a β-blocker, usually given orally, is safe and therefore is recommended as first-line treatment to control ventricular rate, provided the patient is euvolemic. • For patients in NYHA Class I–III, digoxin should be considered when ventricular rate remains high despite β-blockers or when β-blockers are not tolerated or contraindicated. • Treatment with dronedarone to improve ventricular rate control is not recommended due to safety concerns. <u>Recommendations for cardiac imaging in patients with suspected or established heart failure</u>

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	• Transthoracic Echocardiogram (TTE) is recommended for the assessment of myocardial structure and function in subjects with suspected HF in order to establish a diagnosis of HFrEF, HFmrEF, or HFpEF. • TTE is recommended for the assessment of LVEF in order to identify patients with HF who would be suitable for evidence-based pharmacological and device treatment recommended for HFrEF. Recommendations aiming to prevent or delay the development of overt heart failure or prevent death before the onset of symptoms • Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life. • ACE inhibitor is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction in order to prevent or delay the onset of HF and prolong life. • Beta-blocker is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction, in order to prevent or delay the onset of HF and prolong life. Pharmacological treatments indicated in patients with symptomatic 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 β-blocker is recommended, in addition to an ACE inhibitor, for patients with stable, symptomatic HFrEF to reduce the risk of HF hospitalization and death. • A mineralocorticoid receptor antagonist 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. Other pharmacological treatments recommended in selected patients with symptomatic heart failure with reduced ejection fraction • Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion. • 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. Treatments (or combinations of treatments) that may cause harm in patients with symptomatic (New York Heart Association Class II–IV) heart failure with reduced ejection fraction • Diltiazem or verapamil are not recommended in patients with HFrEF, as they increase the risk of HF worsening and HF hospitalization. • The addition of an ARB (or a renin inhibitor) to the combination of an ACE inhibitor and a mineralocorticoid receptor antagonist is not recommended in patients with HF, because of the increased risk of renal dysfunction and hyperkalemia. Not-recommended treatments of co-morbidities in patients with heart failure • Thiazolidinediones (glitazones) are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization. • NSAIDs or COX-2 inhibitors are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization. Recommendations for the management of patients with acute heart failure – pharmacotherapy

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	• 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. • In patients with new-onset AHF or those with chronic, decompensated HF not receiving oral diuretics the initial recommended dose should be 20 to 40 mg intravenous furosemide (or equivalent); for those on chronic diuretic therapy, initial intravenous dose should be at least equivalent to oral dose. • It is recommended to give diuretics either as intermittent boluses or a continuous infusion, and the dose and duration should be adjusted according to the patients' symptoms and clinical status. • Inotropic agents are not recommended unless the patient is symptomatically hypotensive or hypoperfused because of safety concern.
American Heart Association/ American College of Cardiology/ Heart Rhythm Society: **Guideline for the Management of Patients with Atrial Fibrillation (2014)**[26]	Recommendations for risk-based antithrombotic therapy: Class I • In patients with atrial fibrillation (AF), antithrombotic therapy should be individualized based on shared decision-making after discussion of the absolute and relative risks of stroke, bleeding and the patient's values and preferences (Level of Evidence: C). • Selection of antithrombotic therapy should be based on the risk of thromboembolism irrespective of whether the AF patter is paroxysmal, persistent, or permanent (Level of Evidence: B). • In patients with nonvalvular AF, the CHA_2DS_2-VASc score is recommended for assessment of stroke risk (Level of Evidence: B). • For patients with AF who have mechanical heart valves, warfarin is recommended and the target international normalized ratio (INR) should be based on type and location of the prosthesis (Level of Evidence: B). • For patients with nonvalvular AF with prior stroke, TIA, or a CHA_2DS_2-VASc score ≥2, oral anticoagulants are recommended. Options include warfarin (INR 2.0 to 3.0) (Level of Evidence: A), dabigatran, rivaroxaban, or apixaban (Level of Evidence: B). • For patients treated with warfarin, the INR should be determined at least weekly during initiation of antithrombotic therapy and at least monthly when anticoagulation (INR in range) is stable (Level of Evidence: A) • For patients with nonvalvular AF unable to maintain a therapeutic INR level with warfarin, use of a direct thrombin or factor Xa inhibitor is recommended (Level of Evidence: C). • Re-evaluation of the need for and choice of antithrombotic therapy at periodic intervals is recommended to reassess stroke and bleeding risks (Level of Evidence: C). • Bridging therapy with UFH or LMWH is recommended for patients with AF and a mechanical heart valve undergoing procedures that require interruption of warfarin. Decisions regarding bridging therapy should balance the risks of stroke and bleeding (Level of Evidence: C). • For patients with AF without mechanical heart valves who require interruption of warfarin or newer anticoagulants for procedures, decisions about bridging therapy (LMWH or UFH) should balance the risks of stroke and bleeding and the duration of time a patient will not be anticoagulated (Level of Evidence: C). • Renal function should be evaluated prior to initiation of direct thrombin or factor Xa inhibitors and should be re-evaluated when clinically indicated and at least annually (Level of Evidence: B). • For patients with atrial flutter, antithrombotic therapy is recommended according to the same risk profile used for AF (Level of Evidence: C). Class IIa

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	• For patients with nonvalvular AF and a CHA_2DS_2-VASc score of 0, it is reasonable to omit antithrombotic therapy (Level of Evidence: B). • For patients with nonvalvular AF with a CHA_2DS_2-VASc score of ≥2 and who have end-stage chronic kidney disease (creatine clearance <15 mL/min) or who are on hemodialysis, it is reasonable to prescribe warfarin (INR 2.0 to 3.0) for oral anticoagulation (Level of Evidence: B). Class IIb • For patients with nonvalvular AF and a CHA_2DS_2-VASc score of 1, no antithrombotic therapy or treatment with an oral anticoagulant or aspirin may be considered (Level of Evidence: C). • For patients with nonvalvular AF and moderate-to-severe chronic kidney disease with a CHA_2DS_2-VASc score of ≥2, treatment with reduced doses of direct thrombin or factor Xa inhibitors may be considered (e.g., dabigatran, rivaroxaban, or apixaban), but safety and efficacy have not been established (Level of Evidence: C). • In patients with AF undergoing PCI, bare-metal stents may be considered to minimize the required duration of dual antiplatelet therapy. Anticoagulation may be interrupted at the time of the procedure to reduce the risk of bleeding ant the site of peripheral arterial puncture (Level of Evidence: C). • Following coronary revascularization (percutaneous or surgical) in patients with AF and a CHA_2DS_2-VASc score of ≥2, it may be reasonable to use clopidogrel (75 mg once daily) concurrently with oral anticoagulants but without aspirin (Level of Evidence: B). Class III: No Benefit • The direct thrombin inhibitor, dabigatran, and the factor Xa inhibitor, rivaroxaban, are not recommended in patients with AF and end-stage chronic kidney disease or on hemodialysis because of the lack of evidence from clinical trials regarding the balance of risks and benefits (Level of Evidence: C). Class III: Harm • The direct thrombin inhibitor, dabigatran, should not be used in patients with AF and a mechanical heart valve (Level of Evidence: B). <u>Recommendations for rate control:</u> Class I • Control of the ventricular rate using a β-blocker or nondihydropyridine (non-DHP) calcium channel blocker (CCB) is recommended for patients with paroxysmal, persistent, or permanent AF (Level of Evidence: B). • Intravenous administration of a β-blocker or non-DHP CCB is recommended to slow the ventricular heart rate in the acute setting in patients without pre-excitation. In hemodynamically unstable patients, electrical cardioversion is indicated (Level of Evidence: B). • In patients who experience AF-related symptoms during activity, the adequacy of heart rate control should be assessed during exertion, adjusting pharmacological treatment as necessary to keep the ventricular rate within the physiological range (Level of Evidence: C). Class IIa • A heart rate control (resting heart rate <80 beats per minute [bpm]) strategy is reasonable for symptomatic management of AF (Level of Evidence: B). • Intravenous amiodarone can be useful for rate control in critically ill patients without pre-excitation (Level of Evidence: B). • Atrioventricular (AV) nodal ablation with permanent ventricular pacing is reasonable to control heart rate when pharmacological therapy is inadequate and rhythm control is not achievable (Level of Evidence: B). Class IIb • A lenient rate-control strategy (resting heart rate <110 bpm) may be reasonable as

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	long as patients remain asymptomatic and left ventricular systolic function is preserved (Level of Evidence: B). • Oral amiodarone may be useful for ventricular rate control when other measures are unsuccessful or contraindicated (Level of Evidence: C). Class III: Harm • AV nodal ablation with permanent ventricular pacing should not be performed to improve rate control without prior attempts to achieve rate control with medications (Level of Evidence: C). • Non-DHP CCBs should not be used in patients with decompensated HF as these may lead to further hemodynamic compromise (Level of Evidence: C). • In patients with pre-excitation and AF, digoxin, non-DHP CCBs, or intravenous amiodarone should not be administered as they may increase the ventricular response and may result in ventricular fibrillation. (Level of Evidence: B). • Dronedarone should not be used to control the ventricular rate in patients with permanent AF as it increases the risk of the combined endpoint of stroke, myocardial infarction, systemic embolism, or cardiovascular death (Level of Evidence: B). <u>Recommendations for Thromboembolism Prevention</u>: Class I • For patients with AF or atrial flutter of 48-hour duration or longer, or when the duration of AF is unknown, anticoagulation with warfarin (INR 2.0 to 3.0) is recommended for at least three weeks prior to and four weeks after cardioversion, regardless of the CHA_2DS_2-VASc score and the method used to restore sinus rhythm (Level of Evidence: B). • For patients with AF or atrial flutter of more than 48 hours duration that requires immediate cardioversion for hemodynamic instability, anticoagulation should be initiated as soon as possible and continued for at least four weeks after cardioversion unless contraindicated (Level of Evidence: C). • For patients with AF or atrial flutter of less than 48-hour duration and with high risk stroke, intravenous heparin or LMWH, or administration of a factor Xa or direct thrombin inhibitor, is recommended as soon as possible before or immediately after cardioversion, followed by long-term anticoagulation therapy (Level of Evidence: C). • Following cardioversion for AF of any duration, the decision regarding long-term anticoagulation therapy should be based on the thromboembolic risk profile (Level of Evidence: C). Class IIa • For patients with AF or atrial flutter of 48-hour duration or longer or of unknown duration who have not been anticoagulated for the preceding three weeks, it is reasonable to perform a TEE prior to cardioversion and proceed with cardioversion if no LA thrombus is identified, including in the LAA, provided that anticoagulation is achieved before TEE and maintained after cardioversion for at least four weeks (Level of Evidence: B). • For patients with AF or atrial flutter of 48-hour duration or longer, or when the duration of AF is unknown, anticoagulation with dabigatran, rivaroxaban, or apixaban is reasonable for at least three weeks prior to and four weeks after cardioversion (Level of Evidence: C). Class IIb • For patients with AF or atrial flutter of less than 48-hour duration who are at low thromboembolic risk, anticoagulation (heparin, LMWH, or a new oral anticoagulant) or no antithrombotic therapy may be considered for cardioversion, without the need for post cardioversion oral anticoagulation (Level of Evidence: C).

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	<u>Recommendations for pharmacological cardioversion</u>
	Class I
	• Flecainide, dofetilide, propafenone, and intravenous ibutilide are useful for pharmacological cardioversion of AF or atrial flutter, provided contraindications to the selected drug are absent (Level of Evidence: A).
	Class IIa
	• Administration of oral amiodarone is a reasonable option for pharmacological cardioversion of AF (Level of Evidence: A).
	• Propafenone or flecainide ("pill-in-the-pocket") in addition to a β-blocker or non-DHP CCB is reasonable to terminate AF outside the hospital once this treatment has been observed to be safe in a monitored setting for selected patients (Level of Evidence: B).
	Class III: Harm
	• Dofetilide therapy should not be initiated out of hospital because of the risk of excessive QT prolongation that can cause torsades de pointes (Level of Evidence: B).
	
	<u>Recommendations for antiarrhythmic drugs to maintain sinus rhythm</u>
	Class I
	• Before initiating antiarrhythmic drug therapy, treatment of precipitating or reversible causes of AF is recommended (Level of Evidence: C).
	• The following antiarrhythmic drugs are recommended in patients with AF to maintain sinus rhythm, depending on underlying heart disease and comorbidities (Level of Evidence: A):
	  ○ Amiodarone
	  ○ Dofetilide
	  ○ Dronedarone
	  ○ Flecainide
	  ○ Propafenone
	  ○ Sotalol
	• The risks of the antiarrhythmic drug, including proarrhythmia, should be considered before initiating therapy with each drug (Level of Evidence: C).
	• Because of its potential toxicities, amiodarone should only be used after consideration of risks and when other agents have failed or are contraindicated (Level of Evidence: C).
	Class IIa
	• A rhythm-control strategy with pharmacological therapy can be useful in patients with AF for the treatment of tachycardia-induced cardiomyopathy (Level of Evidence: C).
	Class IIb
	• It may be reasonable to continue current antiarrhythmic drug therapy in the setting of infrequent, well-tolerated recurrences of AF when the drug has reduced the frequency or symptoms of AF (Level of Evidence: C).
	Class III: Harm
	• Antiarrhythmic drugs for rhythm control should not be continued when AF becomes permanent (Level of Evidence: C), including dronedarone (Level of Evidence: B).
	• Dronedarone should not be used for treatment of AF in patients with New York Heart Association class III and IV HF or patients who have had an episode of decompensated HF in the past 4 weeks. (Level of Evidence: B).
	
	<u>Upstream therapy</u>
	Class IIa
	• An angiotensin-converting enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB) is reasonable for primary prevention of new-onset AF in patients with HF

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	with reduced left ventricular ejection fraction (Level of Evidence: B). Class IIb • Therapy with an ACE inhibitor or ARB may be considered for primary prevention of new-onset AF in the setting of hypertension (Level of Evidence: B). • Statin therapy may be reasonable for primary prevention of new-onset AF after coronary artery surgery (Level of Evidence: A). Class III: No Benefit • Therapy with an ACE inhibitor, ARB, or statin is not beneficial for primary prevention of AF in patients without cardiovascular disease (Level of Evidence: B).

National Institute for Health and Clinical Excellence: **Atrial Fibrillation: The Management of Atrial Fibrillation (2014)**[27]	Interventions to prevent stroke
	• Do not offer stroke prevention to people aged <65 years with atrial fibrillation (AF) and no risk factors other than their sex (that is, very low risk of stroke equating to CHA_2DS_2-VASc score of 0 for men or 1 for women).
	• Consider anticoagulation for men with a CHA_2DS_2-VASc score of 1. Take the bleeding risk into account.
	• Offer anticoagulation to people with a CHA_2DS_2-VASc score of 2 or above, taking bleeding risk into account.
	• Discuss the options for anticoagulation with the person and base the choice on their clinical features and preferences.
	• Apixaban
	  ○ Apixaban is recommended as an option for preventing stroke and systemic embolism within its marketing authorization, that is, in people with nonvalvular atrial fibrillation with one or more risk factors such as:
	  ▪ Prior stroke of transient ischemic attack (TIA).
	  ▪ Age 75 years or older.
	  ▪ Hypertension.
	  ▪ Diabetes mellitus.
	  ▪ Symptomatic heart failure.
	• Dabigatran etexilate
	  ○ Dabigatran etexilate is recommended as an option for the prevention of stroke and systemic embolism within its licensed indication, that is, in people with nonvalvular atrial fibrillation with one or more of the following risk factors:
	  ▪ Previous stroke, TIA, or systemic embolism.
	  ▪ Left ventricular ejection fraction (LVEF) <40%.
	  ▪ Symptomatic heart failure (HF) of New York Heart Association (NYHA) class 2 or above.
	  ▪ Age 75 years or older.
	  ▪ Age 65 years or older with one of the following: diabetes mellitus, coronary artery disease, or hypertension.
	• Rivaroxaban
	  ○ Rivaroxaban is recommended as an option for the prevention of stroke and systemic embolism within its licensed indication, that is, in people with nonvalvular AF with one or more risk factors such as:
	  ▪ Congestive heart failure.
	  ▪ Hypertension.
	  ▪ Age 75 years or older.
	  ▪ Diabetes mellitus.
	  ▪ Prior stroke or TIA.
	• The decision about whether to start treatment with a new oral anticoagulant should be made after an informed discussion between the clinician and the person about the risks and benefits of the agent compared with the alternatives, including warfarin. For people who are taking warfarin, the potential risks and benefits of switching to a different oral agent should be considered in light of their level of international normalized ratio (INR) control.

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	<u>Assessing anticoagulation control with vitamin K antagonists</u>
	• Calculate the person's time in therapeutic range (TTR) at each visit. When calculating TTR:
	  o Use a validated method of measurement such as the Rosendaal method for computer-assisted dosing or proportion of tests in range for manual dosing.
	  o Exclude measurements taken during the first six weeks of treatment.
	  o Calculate TTR over a maintenance period of at least six months.
	• Reassess anticoagulation for a person with poor anticoagulation control shown by any of the following:
	  o Two INR values higher than 5 or one INR value higher than 8 within the past six months.
	  o Two INR values less than 1.5 within the past six months.
	  o TTR <65%.
	• When assessing anticoagulation, take into account and if possible address the following factors that may contribute to poor anticoagulation control: Cognitive function, adherence, illness, drug interactions, and lifestyle factors including diet and alcohol consumption.
	• If poor anticoagulation control cannot be improved, evaluate the risks and benefits of alternative stroke prevention strategies and discuss these with the person.
	
	<u>When to offer rate and rhythm control</u>
	• Offer rate control as the first-line strategy to people with AF, except in people whose AF has a reversible cause, who have HF thought to be primarily caused by AF, with new-onset AF, with atrial flutter whose condition is considered suitable for an ablation strategy to restore sinus rhythm, and for whom a rhythm control strategy would be more suitable based on clinical judgement.
	
	<u>Rate control</u>
	• Offer either a standard β-blocker (that is, a β-blocker other than sotalol) or a rate-limiting calcium channel blocker (CCB) as initial monotherapy to people with AF who need drug treatment as part of a rate control strategy. Base the choice of drug on the person's symptoms, heart rate, comorbidities, and preferences when considering drug treatment.
	• Consider digoxin monotherapy for people with non-paroxysmal AF only if they are sedentary.
	• 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.
	
	<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.
	• 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

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	after successful cardioversion in people with paroxysmal or persistent atrial fibrillation: ○ 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 ○ 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 ○ Who do not have left ventricular systolic dysfunction, AND ○ Who do not have a history of, or current, HF. • 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 HF. • 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.
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)[28]**	Recommended prevention strategies for all postoperative atrial fibrillation (POAF) patients • 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. Recommended prevention strategies for intermediate to high-risk POAF patients • 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. Rate control recommendations for patients with new onset POAF • 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.

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	• 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 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

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	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. Management of anticoagulation for new onset POAF • 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 (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)**[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

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	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.
American Society of Hypertension/ International Society of Hypertension: **Clinical Practice Guidelines for the Management of Hypertension in the Community (2014)**[30]	Nonpharmacologic treatment • In patients with hypertension that is no more severe than stage one and is not associated with evidence of abnormal cardiovascular findings or other cardiovascular risks, six to 12 months of lifestyle changes can be attempted in the hope that they may be sufficiently effective to make it unnecessary to use medicines. • It may be prudent to start treatment with drugs sooner if it is clear that the blood pressure is not responding to the lifestyle methods or if other risk factors appear. • Weight loss: In patients who are overweight or obese, weight loss is helpful in treating hypertension, diabetes, and lipid disorders. • Salt reduction: Reduction of salt intake is recommended because it can reduce blood pressure and decrease the need for medications in patients who are "salt sensitive." • Exercise: Regular aerobic exercise can help reduce blood pressure. • Alcohol consumption: Up to two drinks a day can be helpful in protecting against cardiovascular events, but greater amounts of alcohol can raise blood pressure and should therefore be discouraged. In women, alcohol should be limited to one drink a day. • Cigarette smoking: Stopping smoking will not reduce blood pressure, but since smoking by itself is such a major cardiovascular risk factor, patients must be strongly urged to discontinue this habit. Drug treatment of hypertension • Treatment with drugs should be started in patients with blood pressures >140/90 mm Hg in whom lifestyle treatments have not been effective. • In patients with stage two hypertension (blood pressure ≥160/100 mm Hg), drug treatment should be started immediately after diagnosis, usually with a two-drug combination, without waiting to see the effects of lifestyle changes. • For patients older than 80 years, the suggested threshold for starting treatment is at levels ≥150/90 mm Hg. Thus, the target of treatment should be <140/90 mm Hg for most patients but <150/90 mm Hg for older patients (unless these patients have chronic kidney disease or diabetes, when <140/90 mm Hg can be considered). • Most patients will require more than one drug to achieve control of their blood pressure. • In general, increase the dose of drugs or add new drugs at approximately two to three week intervals. This frequency can be faster or slower depending on the judgment of the practitioner. In general, the initial doses of drugs chosen should be at least half of the maximum dose so that only one dose adjustment is required thereafter. It is generally anticipated that most patients should reach an effective

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	treatment regimen, whether one, two, or three drugs, within six to eight weeks.
	• Choice of drugs should be influenced by the age, ethnicity/race, and other clinical characteristics of the patient.
	• The choice of drugs will also be influenced by other conditions (e.g., diabetes and coronary disease) associated with the hypertension. Pregnancy also influences drug choice.
	• Long-acting drugs that need to be taken only once daily are preferred to shorter-acting drugs that require multiple doses because patients are more likely to follow a simple treatment regimen.
	• This guideline only makes recommendations for drug classes, not individual agents. There is an assumption, unless otherwise stated, that all drugs in a class are similar to each other.
	• Drug selectin when hypertension is the only or main concern:
	  ○ For black patients of all ages, use calcium channel blocker (CCB) or thiazide diuretic as first drug, then add angiotensin receptor blocker (ARB) or angiotensin-converting enzyme (ACE) inhibitor if needed.
	  ○ For white and other non-black patients <60 years of age, use ARB or ACE inhibitor as first drug, then add CCB or thiazide diuretic if needed.
	  ○ For white and other non-black patients ≥60 years of age, use CCB or thiazide diuretic as first drug, then add ARB or ACE inhibitor if needed.
	• Drug selection when hypertension is associated with other conditions:
	  ○ For patients with hypertension and diabetes, use ARB or ACE inhibitor as first drug (note, in black patients it is acceptable to start with a CCB or thiazide), then add CCB or thiazide diuretic (unless starting on CCB or thiazide in black patients) if needed.
	  ○ For patients with hypertension and chronic kidney disease, use ARB or ACE inhibitor as first drug, then add CCB or thiazide diuretic if needed.
	  ○ For patients with hypertension and clinical coronary artery disease, use β-blocker plus ARB or ACE inhibitor as first drugs, then add CCB or thiazide diuretic if needed.
	  ○ For patients with hypertension and stroke history, use ACE inhibitor or ARB as first drug, then add thiazide diuretic or CCB if needed.
	• For patients with hypertension and heart failure, patients with h symptomatic heart failure should usually receive an ARB or ACE inhibitor plus β-blocker plus diuretic plus spironolactone regardless of blood pressure. A dihydropyridine CCB can be added if needed for blood pressure control.

Hypertension Canada: **2017 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults (2017)**[31]	<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.
	
	<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). ○ 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>Guidelines for individuals 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).
	
	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.
	
	Treatment of hypertension in association with stroke
	• BP management in acute ischemic stroke (onset to 72 hours)
	  ○ For patients with ischemic stroke not eligible for thrombolytic therapy, treatment of hypertension in the setting of acute ischemic stroke or transient ischemic attack should not be routinely undertaken. Extreme BP increases (e.g., SBP >220 mmHg or DBP >120 mmHg) may be treated to reduce the BP by approximately 15%, and not more than 25%, over the first 24 hours with gradual reduction thereafter. Avoid excessive lowering of BP because this might exacerbate existing ischemia or might induce ischemia, particularly in the setting of intracranial arterial occlusion or extracranial carotid or vertebral artery occlusion. Pharmacological agents and routes of administration should be chosen to avoid precipitous decreases in BP.
	  ○ For patients with ischemic stroke eligible for thrombolytic therapy, very high BP (>185/110 mmHg) should be treated concurrently in patients receiving thrombolytic therapy for acute ischemic stroke to reduce the risk of secondary intracranial hemorrhage.
	• 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

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	recommended. • BP management in hemorrhagic stroke (onset to 72 hours) ○ For patients with intracerebral hemorrhage (ICH) in the hyperacute phase (in the first 24 hours) SBP lowering to <140 mmHg should be avoided because of an absence of benefit (relative to a target of <180 mmHg) and some suggestion of harm. 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 • For patients with nondiabetic chronic kidney disease, target BP is <140/90 mmHg. • For patients with hypertension and proteinuric chronic kidney disease (urinary protein >500 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. • Thiazide/thiazide-like diuretics are recommended as additive antihypertensive therapy. For patients with chronic kidney disease and volume overload, loop diuretics are an alternative. • 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. • In patients with hypertension attributable to FMD-related renal artery stenosis, revascularization should be considered. • 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 2 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. Combination therapy using two first-line agents may also be considered as initial treatment of hypertension if SBP is 20 mmHg greater than target or if DBP is 10 mmHg greater than target. However, caution should be exercised in patients in whom a substantial decrease in BP is more likely or poorly tolerated (e.g., elderly patients and patients with autonomic neuropathy). • For persons with cardiovascular or kidney disease, including microalbuminuria, or

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	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.
European Society of Hypertension/European Society of Cardiology: **2013 Guidelines for the management of arterial hypertension (2013)**[32]	The 2013 guidelines on hypertension of the European Society of Hypertension and the European Society of Cardiology follow the guidelines jointly issued by the two societies in 2003 and 2007. <u>Treatment strategies and choice of antihypertensive drugs</u> • Diuretics (including thiazides, chlorthalidone, and indapamide), β-blockers, calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) are all suitable for the initiation and maintenance of antihypertensive treatment, either as monotherapy or in some combinations. • Some agents should be considered as the preferential choice in specific conditions because used in trials in those conditions or because of greater effectiveness in specific types of organ damage. • Initiation of antihypertensive therapy with a two-drug combination may be considered in patients with markedly high baseline blood pressure (BP) or at high cardiovascular (CV) risk. • The combination of two antagonists of the renin-angiotensin system (RAS) is not recommended and should be discouraged. • Other drug combinations should be considered and probably are beneficial in proportion to the extent of BP reduction. However, combinations that have been successfully used in trials may be preferable. • Combinations of two antihypertensive drugs at fixed doses in a single tablet may be recommended and favored, because reducing the number of daily pills improves adherence, which is low in patients with hypertension. <u>Treatment strategies in white-coat and masked hypertension</u> • In white-coat hypertensives without additional risk factors, therapeutic intervention may be limited to lifestyle changes only, but this decision should be accompanied by close follow-up. • In white-coat hypertensives with a higher CV risk because of metabolic derangements or asymptomatic organ damage, drug treatment may be considered in addition to lifestyle changes. • In masked hypertension, both lifestyle measures and antihypertensive drug treatment should be considered, because this type of hypertension has been consistently found to have a CV risk very close to that of in- and out-of-office hypertension. <u>Antihypertensive treatment strategies in the elderly</u> • In elderly hypertensives with SBP ≥160 mmHg there is solid evidence to recommend reducing SBP to between 150 and 140 mmHg. • In fit elderly patients <80 years old antihypertensive treatment may be considered at SBP values ≥140 mmHg with a target SBP <140 mmHg if treatment is well tolerated. • In individuals older than 80 years with an initial SBP ≥160 mmHg, it is recommended to reduce SBP to between 150 and 140 mmHg, provided they are in good physical and mental conditions.

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	• In frail elderly patients, it is recommended to leave decisions on antihypertensive therapy to the treating physician, and based on monitoring of the clinical effects of treatment. • Continuation of well-tolerated antihypertensive treatment should be considered when a treated individual becomes an octogenarian. • All hypertensive agents are recommended and can be used in the elderly, although diuretics and calcium antagonists may be preferred in isolated systolic hypertension. <u>Treatment strategies in hypertensive women</u> • Hormone therapy and selective estrogen receptor modulators are not recommended and should not be used for primary or secondary prevention of CVD. • If treatment of younger perimenopausal women is considered for severe menopausal symptoms, the benefits should be weighed against potential risks. • Drug treatment of severe hypertension in pregnancy (SBP >160 mmHg or DBP >110 mmHg) is recommended. • Drug treatment may also be considered in pregnant women with persistent elevation of BP ≥150/95 mmHg, and in those with BP ≥140/90 mmHg in the presence of gestational hypertension, subclinical organ damage or symptoms. • In women at high risk of pre-eclampsia, provided they are at low risk of gastrointestinal hemorrhage, treatment with low dose aspirin from 12 weeks until delivery may be considered. • In women with child-bearing potential RAS blockers are not recommended and should be avoided. • Methyldopa, labetalol, and nifedipine should be considered preferential antihypertensive drugs in pregnancy. Intravenous labetalol or infusion of nitroprusside should be considered in case of emergency (pre-eclampsia). <u>Treatment strategies in patients with diabetes</u> • While initiation of antihypertensive drug treatment in diabetic patients whose SBP is ≥160 mmHg is mandatory, it is strongly recommended to start drug treatment also when SBP is ≥140 mmHg. • A SBP goal <140 mmHg is recommended in patients with diabetes. • The DBP target in patients with diabetes is recommended to be <85 mmHg. • All classes of antihypertensive agents are recommended and can be used in patients with diabetes; RAS blockers may be preferred, especially in the presence of proteinuria or microalbuminuria. • It is recommended that individual drug choice takes comorbidities into account. • Simultaneous administration of two blockers of the RAS is not recommended and should be avoided in patients with diabetes <u>Treatment strategies in hypertensive patients with metabolic syndrome</u> • Lifestyle changes, particularly weight loss and physical exercise, are to be recommended to all individuals with the metabolic syndrome. These interventions improve not only BP, but the metabolic components of the syndrome and delay diabetes onset. • As the metabolic syndrome can be considered a 'pre-diabetic' state, antihypertensive agents potentially improving or at least not worsening insulin sensitivity, such as RAS blockers and calcium antagonists, should be considered as the preferred drugs. Beta-blockers (with the exception of vasodilating β-blockers) and diuretics should be considered only as additional drugs, preferably in association with a potassium-sparing agent. • It is recommended to prescribe antihypertensive drugs with particular care in hypertensive patients with metabolic disturbances when BP is ≥140/90 mmHg after a suitable period of lifestyle changes, and to maintain BP <140/90 mmHg.

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	• BP lowering drugs are not recommended in individuals with metabolic syndrome and high normal BP. Therapeutic strategies in hypertensive patients with nephropathy • Lowering SBP to <140 mmHg should be considered. • When overt proteinuria is present, SBP values <130 mmHg may be considered, provided that changes in eGFR are monitored. • RAS blockers are more effective in reducing albuminuria than other antihypertensive agents, and are indicated in hypertensive patients in the presence of microalbuminuria or overt proteinuria. • Reaching BP goals usually requires combination therapy, and it is recommended to combine RAS blockers with other antihypertensive agents. • Combination of two RAS blockers, though potentially more effective in reducing proteinuria, is not recommended. • Aldosterone antagonists cannot be recommended in chronic kidney disease (CKD), especially in combination with a RAS blocker, because of the risk of excessive reduction in renal function and of hyperkalemia. Therapeutic strategies in hypertensive patients with cerebrovascular disease • It is not recommended to intervene with BP-lowering therapy during the first week after acute stroke irrespective of BP level, although clinical judgement should be used in the face of very high SBP values. • Antihypertensive treatment is recommended in hypertensive patients with a history of stroke or transient ischemic attack (TIA), even when initial SBP is in the 140 to 159 mmHg range. • In hypertensive patients with a history of stroke or TIA, a SBP goal of <140 mmHg should be considered. • In elderly hypertensives with previous stroke or TIA, SBP values for intervention and goal may be considered to be somewhat higher. • All drug regimens are recommended for stroke prevention, provided that BP is effectively reduced. Therapeutic strategies in hypertensive patients with heart disease • In hypertensive patients with CHD, a SBP goal <140 mmHg should be considered. • In hypertensive patients with a recent myocardial infarction, β-blockers are recommended. In case of other CHD all antihypertensive agents can be used, but β-blockers and calcium antagonists are to be preferred for symptomatic reasons (angina). • Diuretics, β-blockers, ACE inhibitors, angiotensin receptor blockers, and/or mineralocorticoid receptor antagonists are recommended in patients with heart failure or severe left ventricular (LV) dysfunction to reduce mortality and hospitalization. • In patients with heart failure and preserved ejection fraction (EF), there is no evidence that antihypertensive therapy per se or any particular drug is beneficial. However, in these patients, as well as in patients with hypertension and systolic dysfunction, lowering SBP to around 140 mmHg should be considered. Treatment guided by relief of symptoms (congestion with diuretics, high heart rate with β-blockers, etc.) should also be considered. • ACE inhibitors and angiotensin receptor blockers (and β-blockers and mineralocorticoid receptor antagonists if heart failure coexists) should be considered as antihypertensive agents in patients at risk of new or recurrent atrial fibrillation. • It is recommended that all patients with left ventricular hypertrophy (LVH) receive antihypertensive agents. • In patients with LVH, initiation of treatment with one of the agents that have shown

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	a greater ability to regress LVH should be considered, i.e. ACE inhibitors, angiotensin receptor blockers, and calcium antagonists. Therapeutic strategies in hypertensive patients with atherosclerosis, arteriosclerosis, and peripheral artery disease (PAD) • In the presence of carotid atherosclerosis, prescription of calcium antagonists and ACE inhibitors should be considered as these agents have shown a greater efficacy in delaying atherosclerosis progression than diuretics and β-blockers. • In hypertensive patients with a pulse wave velocity above 10 m/s, all antihypertensive drugs should be considered provided that a BP reduction to <140/90 mmHg is consistently achieved. • Antihypertensive therapy is recommended in hypertensive patients with PAD to achieve a goal of <140/90 mmHg, because of their high risk of myocardial infarction, stroke, heart failure, and CV death. • Though a careful follow up is necessary, β-blockers may be considered for the treatment of arterial hypertension in patients with PAD, since their use does not appear to be associated with exacerbation of PAD symptoms.

National Institute for Health and Clinical Excellence: **Hypertension in adults: diagnosis and management (2011)**[33]
 	
Reaffirmed Nov 2016
	Choosing antihypertensive drug treatment
	• 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 people ≥80 years of age the same antihypertensive drug treatment as people aged 55 to 80 years, taking into account any comorbidities.
	• Offer antihypertensive drug treatment to women of child-bearing potential in line with the recommendations on Management of pregnancy with chronic hypertension and Breastfeeding in 'Hypertension in pregnancy' (NICE clinical guideline 107).
	
	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). 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 step one antihypertensive (ACE inhibitor, ARB) with a calcium channel blocker (CCB) to patients >55 years of age and to black patients of African or Caribbean family origin 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 chlorthalidone (12.5 to 25.0 mg once daily) or indapamide (1.5 mg modified-release once daily or 2.5 mg once daily) in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide.
	• For patients who are already receiving treatment with bendroflumethiazide or hydrochlorothiazide and whose blood pressure is stable and well controlled, continue treatment as is.
	• β-blockers are not a preferred initial therapy for hypertension; however, β-blockers may be considered in younger patients, particularly:
	  ○ Patients with an intolerance or contraindication to ACE inhibitors and ARBs.
	  ○ Women of child-bearing potential.
	  ○ People with evidence of increased sympathetic drive.
	• If treatment is initiated with a β-blocker and a second antihypertensive is required, add a CCB over a thiazide-like diuretic to reduce the risk of developing diabetes.

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	Step two treatment
	• If blood pressure is not controlled with a step one antihypertensive, offer a step two treatment with a CCB in combination with an ACE inhibitor or an ARB.
	• If a CCB is not appropriate or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic.
	• For black patients of African or Caribbean family origin, consider an ARB in preference to an ACE inhibitor, in combination with a CCB.
	
	Step three treatment
	• Before considering step three treatment, review medication to ensure step two treatment is at optimal or best tolerated doses.
	• If three drugs are required to control blood pressure, the combination of an ACE inhibitor or ARB, CCB, and thiazide-like diuretic should be utilized.
	
	Step four treatment
	• Regard clinic blood pressure that remains >140/90 mmHg after treatment with the optimal or best tolerated doses of an ACE inhibitor or an ARB plus a CCB plus a diuretic as resistant hypertension, and consider adding a fourth antihypertensive drug and/or seeking expert advice.
	• For treatment of resistant hypertension at step four:
	  ○ Consider further diuretic therapy with low-dose spironolactone (25 mg once daily) if the blood potassium level is 4.5 mmol/l or lower. Use particular caution in people with a reduced estimated glomerular filtration rate because they have an increased risk of hyperkalemia.
	  ○ Consider higher-dose thiazide-like diuretic treatment if the blood potassium level is higher than 4.5 mmol/l.
	  ○ If further diuretic therapy for resistant hypertension is not tolerated or is contraindicated or ineffective, consider an α-blocker or β-blocker.

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**	Blood pressure management in chronic kidney disease (CKD) non-dialysis (ND) patients without diabetes mellitus • The Work Group recommends that non-diabetic adults with CKD ND and urine albumin excretion <30 mg per 24 hours (or equivalent*) whose office blood

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Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease (2012)[35]	pressure is consistently >140 mm Hg systolic or >90 mm Hg diastolic be treated with blood pressure -lowering drugs to maintain a blood pressure that is consistently ≤140 mm Hg systolic and ≤90 mm Hg diastolic. • The Work Group suggests that non-diabetic adults with CKD ND and urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with BP-lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic. • The Work Group suggests that non-diabetic adults with CKD ND and urine albumin excretion >300 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with blood pressure -lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤ 80 mm Hg diastolic. • The Work Group suggests that an angiotensin receptor blocker (ARB) or angiotensin converting enzyme inhibitor (ACE-I) be used in non-diabetic adults with CKD ND and urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*) in whom treatment with blood pressure -lowering drugs is indicated. • The Work Group recommends that an ARB or ACE-I be used in non-diabetic adults with CKD ND and urine albumin excretion >300 mg per 24 hours (or equivalent*) in whom treatment with blood pressure -lowering drugs is indicated. <u>Blood pressure management in CKD ND patients with diabetes mellitus</u> • The Work Group recommends that adults with diabetes and CKD ND with urine albumin excretion <30 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >140 mm Hg systolic or >90 mm Hg diastolic be treated with BP-lowering drugs to maintain a blood pressure that is consistently ≤140 mm Hg systolic and ≤90 mm Hg diastolic. • The Work Group suggests that adults with diabetes and CKD ND with urine albumin excretion >30 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with BP-lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic. • The Work Group suggests that an ARB or ACE-I be used in adults with diabetes and CKD ND with urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*). • The Work Group recommends that an ARB or ACE-I be used in adults with diabetes and CKD ND with urine albumin excretion >300 mg per 24 hours (or equivalent*). <u>Blood pressure management in kidney transplant recipients (non–dialysis-dependent CKD of any stage with a kidney transplant [CKD T])</u> • The Work Group suggests that adult kidney transplant recipients whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic, irrespective of the level of urine albumin excretion. • In adult kidney transplant recipients, choose a blood pressure -lowering agent after taking into account the time after transplantation, use of calcineurin inhibitors, presence or absence of persistent albuminuria, and other co morbid conditions. <u>Blood pressure management in children with CKD ND</u> • The Work Group recommends that in children with CKD ND, blood pressure -lowering treatment is started when blood pressure is consistently above the 90th percentile for age, sex, and height. • The Work Group suggests that in children with CKD ND (particularly those with proteinuria), blood pressure is lowered to consistently achieve systolic and diastolic

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	readings less than or equal to the 50th percentile for age, sex, and height, unless achieving these targets is limited by signs or symptoms of hypotension. • The Work Group suggests that an ARB or ACE-I be used in children with CKD ND in whom treatment with blood pressure -lowering drugs is indicated, irrespective of the level of proteinuria. Blood pressure management in elderly persons with CKD ND • Tailor blood pressure treatment regimens in elderly patients with CKD ND by carefully considering age, co-morbidities and other therapies, with gradual escalation of treatment and close attention to adverse events related to blood pressure treatment, including electrolyte disorders, acute deterioration in kidney function, orthostatic hypotension and drug side effects. *Approximate equivalents for albumin excretion rate per 24 hours is expressed as protein excretion rate per 24 hours, albumin/creatinine ratio, protein/creatinine ratio, and protein reagent strip results.
American Diabetes Association: **Standards of Medical Care in Diabetes (2017)**[36]	Hypertension/blood pressure control • Blood pressure should be measured at every routine visit. Patients found to have elevated blood pressure should have blood pressure confirmed on a separate day. • Most patients with diabetes and hypertension should be treated to a systolic blood pressure goal of <140 mmHg and a diastolic blood pressure goal of <90 mmHg. • Lower systolic and diastolic blood pressure targets, such as 130/80 mmHg, may be appropriate for individuals at high risk of cardiovascular disease, if they can be achieved without undue treatment burden. • In pregnant patients with diabetes and chronic hypertension, blood pressure targets of 120 to 160/80 to 105 mmHg are suggested in the interest of optimizing long-term maternal health and minimizing impaired fetal growth. • Patients with confirmed office-based blood pressure >140/90 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). 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. • For patients with blood pressure >120/80 mmHg, lifestyle intervention consists of weight loss if overweight or obese; a Dietary Approaches to Stop Hypertension–style dietary pattern including reducing sodium and increasing potassium intake; moderation of alcohol intake; and increased physical activity. Coronary heart disease • In asymptomatic patients, routine screening for coronary artery disease is not

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	recommended as it does not improve outcomes as long as atherosclerotic cardiovascular disease risk factors are treated. • Consider investigations for coronary artery disease in the presence of any of the following: atypical cardiac symptoms (e.g., unexplained dyspnea, chest discomfort); signs or symptoms of associated vascular disease including carotid bruits, transient ischemic attack, stroke, claudication, or peripheral arterial disease; or electrocardiogram abnormalities (e.g., Q waves). • In patients with known atherosclerotic cardiovascular disease, use aspirin and statin therapy (if not contraindicated) and consider ACE inhibitor therapy to reduce the risk of cardiovascular events. • In patients with prior myocardial infarction, β-blockers should be continued for at least two years after the event. • In patients with symptomatic heart failure, thiazolidinedione treatment should not be used. • In patients with type 2 diabetes with stable congestive heart failure, metformin may be used if estimated glomerular filtration remains >30 mL/min but should be avoided in unstable or hospitalized patients with congestive heart failure. <u>Diabetic 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, in all patients with type 2 diabetes, and in all patients with comorbid hypertension. • Optimize glucose control to reduce the risk or slow the progression of diabetic kidney disease. • Optimize blood pressure control to reduce the risk or slow the progression of diabetic kidney disease. • For people with nondialysis-dependent diabetic kidney disease, dietary protein intake should be approximately 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. • 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) B 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 or changes in potassium when ACE inhibitors, angiotensin receptor blockers, or diuretics are used. • Continued monitoring of urinary albumin–to–creatinine ratio in patients with albuminuria treated with an ACE inhibitor or an angiotensin receptor blocker is reasonable to assess the response to treatment and progression of diabetic kidney disease. • An ACE inhibitor or an angiotensin receptor blocker is not recommended for the primary prevention of diabetic kidney disease 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. • When estimated glomerular filtration rate is <60 mL/min/1.73 m^2, evaluate and manage potential complications of chronic kidney disease. • Patients should be referred for evaluation for renal replacement treatment if they have an estimated glomerular filtration rate <30 mL/min/1.73 m^2. • Promptly refer to a physician experienced in the care of kidney disease 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[1,2,6-14]

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.

Generic Name(s)	Interaction	Mechanism
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 (diltiazem, verapamil)	Ibrutinib	Diltiazem inhibits CYP3A4 metabolism of ibrutinib, thereby increasing plasma concentrations, pharmacologic effects, and risk of toxicity (e.g., hemorrhage, renal toxicity).
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	β-Blockers	Increased serum levels of β-blockers may result if

Generic Name(s)	Interaction	Mechanism
blocking agents, miscellaneous (diltiazem)		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)	Theophllines	The pharmacologic and toxic effects of theophyllines may be increased due to the inhibition of metabolism of theophylline by diltiazem.
Calcium-channel blocking agents, miscellaneous (verapamil)	β-Blockers	Effects of β-blockers and diltiazem may be increased, close 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.

Generic Name(s)	Interaction	Mechanism
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[1,2,6-14]

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

Adverse Events	Diltiazem	Verapamil
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		
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

Adverse Events	Diltiazem	Verapamil
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	-	✔
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[1,2,8-18]

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	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

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	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		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
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.[37] (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.[38] (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.[39] (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.[40] (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.[41] (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.[42] (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.[43] (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.[44] (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.[45] (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.[46] (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.[47] (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.[48] (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.[49] (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.[50] (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.[51] (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.[52] (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.[53] (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.[54] (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.[55] (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.[56] (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.[57] (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.[58] (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.[59] (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.[60] (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.[61] (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.[62] (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®*, Calan SR®*, Verelan®*, Verelan PM®*	$$$$$	$$

*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.[1,2,6-14] 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. It should be noted that the verapamil and trandolapril fixed-dose combination product is included in the angiotensin converting enzyme inhibitor class review (AHFS Class 243204).

There are several national and international guidelines that provide recommendations regarding the use of calcium-channel blocking agents.[15-36] 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.[15-20] Calcium-channel blocking agents are recommended as initial therapy in patients with variant/vasospastic angina.[16,19] Verapamil may be considered for secondary prevention of cardiovascular disease in patients with no heart failure in whom β-blockers are contraindicated.[21] 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.[26-28] 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; however, verapamil and diltiazem may be considered in patients with preserved left ventricular ejection fraction who have atrial fibrillation requiring ventricular rate control (with intolerance to β-blockers), angina, or hypertension.[22-24] 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.[29-35] Most patients will require more than one antihypertensive medication to achieve blood pressure goals.[29-35]

Clinical trials demonstrate that diltiazem and verapamil can effectively treat angina and improve blood pressure.[37-41,53-61] Both agents have been shown to reduce mortality and cardiovascular event rates compared to placebo.[43] 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.[44-50]

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
November 8, 2017

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.[3-20] 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.[3-20] The ACE inhibitors are available as single entity products, as well as in combination with hydrochlorothiazide or verapamil. 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. Verapamil dilates coronary and peripheral arteries. It also slows conduction through the AV node, and has negative inotropic and chronotropic effects.[19,20]

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 August 2015.

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	Aceon®*	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

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Lisinopril and hydrochlorothiazide	tablet	Prinzide®*, Zestoretic®*	lisinopril and hydrochlorothiazide
Moexipril and hydrochlorothiazide	tablet	N/A	moexipril and hydrochlorothiazide
Quinapril and hydrochlorothiazide	tablet	Accuretic®*	quinapril and hydrochlorothiazide
Trandolapril and verapamil	extended-release tablet	Tarka®*	trandolapril and verapamil

*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 College of Cardiology/American Heart Association: **2007 Chronic Angina Focused Update of the 2002 Guidelines for the Management of Patients With Chronic Stable Angina (2007)**[21]	• Aspirin should be started at 75 to 162 mg/day and continued indefinitely in all patients, unless contraindicated. • Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with an increased risk of bleeding and should be monitored closely. • Patients with hypertension and established coronary artery disease (CAD) should be treated with blood pressure medication(s) as tolerated, including angiotensin-converting enzyme inhibitors (ACE inhibitors) and/or β-adrenergic antagonists (β-blockers) with the addition of other medications as needed to achieve blood pressure goals of <140/90 or <130/80 mm Hg for patients with chronic kidney disease or diabetes. • Long-acting calcium-channel blocking agents or long-acting nitrates may be used if β-blockers are contraindicated. Immediate-release and short-acting dihydropyridine calcium channel blockers can increase adverse cardiac events and should not be used. • Long-acting calcium channel blockers or long-acting nitrates may be used with β-blockers if initial treatment is not successful. • ACE inhibitors should be used indefinitely in patients with a left ventricular ejection fraction (LVEF) of ≤40% and in those with hypertension, diabetes or chronic kidney disease, unless contraindicated. • ACE inhibitors should also be used indefinitely in patients at lower risk (mildly reduced or normal LVEF in whom cardiovascular risk factors remain well controlled and revascularization has been performed), unless contraindicated. • Angiotensin II receptor blockers (ARBs) are recommended in patients with hypertension, those who have an indication for an ACE inhibitor and are intolerant to them, who have heart failure, or who have had a myocardial infarction (MI) and have a LVEF of ≤40%. • ARBs may be considered in combination with an ACE inhibitor for heart failure due to left ventricular systolic dysfunction. • Aldosterone blockade is recommended in patients post-MI without significant renal dysfunction or hyperkalemia who are already receiving therapeutic doses of an ACE inhibitor and a β-blocker, have a LVEF ≤40% and have either diabetes or heart failure. • It is beneficial to start and continue β-blocker therapy indefinitely in all patients who have had a MI, acute coronary syndrome or left ventricular dysfunction with or without heart failure symptoms, unless contraindicated.

Clinical Guideline	Recommendations
	• Annual influenza vaccination is recommended in patients with cardiovascular disease.
European Society of Cardiology: **Guidelines on the Management of Stable Coronary Artery Disease (2013)**[22]	<u>General management of stable coronary artery disease (SCAD) patients</u> • The goal of management of SCAD is to reduce symptoms and improve prognosis. • The management of CAD patients encompasses lifestyle modification, control of CAD risk factors, evidence-based pharmacological therapy, and patient education. <u>General considerations for pharmacological treatments in SCAD patients</u> • 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. <u>Pharmacological treatments for angina/ischemia relief in SCAD patients</u> • Short-acting nitrates are recommended. • First-line treatment is indicated with ß-blockers and/or calcium channel blockers to control heart rate and symptoms. • For second-line treatment it is recommended to add long-acting nitrates or ivabradine or nicorandil* or ranolazine, according to heart rate, blood pressure, and tolerance. • For second-line treatment, trimetazidine* may be considered. • 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 β-blockers avoided. <u>Pharmacological treatments for event prevention in SCAD patients</u> • Low-dose aspirin daily is recommended in all SCAD patients. • Clopidogrel is indicated as an alternative in case of aspirin intolerance. • Statins are recommended in all SCAD 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. • β-blockers are recommended as a first line treatment. • Calcium antagonists are recommended if β-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 (aminophylline, bamiphylline*) or non-pharmacological treatments such as neurostimulatory techniques may be considered in patients with symptoms refractory to the above listed drugs.
American College of Physicians/ American College of Cardiology Foundation/ American Heart Association/ American Association	<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.

Clinical Guideline	Recommendations
for Thoracic Surgery/ Preventive Cardiovascular Nurses Association/ Society of Thoracic Surgeons: **Management of Stable Ischemic Heart Disease (2012)**[23]	• 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 Management of Patients With Non–ST-Elevation Acute Coronary Syndromes (2014)**[24]	<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
	  ○ 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,

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	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 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

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	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. ○ 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

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	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 patients treated with ticagrelor and 81 to 325 mg daily in all other patients. ○ 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. ○ 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 ○ 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. ○ 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: **Guideline for the Management of**	<u>Pharmacological treatment of ischemia</u> • Early initiation of β-blocker treatment is recommended in patients with ongoing ischemic symptoms and without contraindications. • Sublingual or intravenous nitrates are recommended to relieve angina;

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Acute Coronary Syndromes in Patients Presenting Without Persistent ST-Segment Elevation (2015)[25]	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.
	  ○ 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.
	• 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

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	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. 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 CHADS2-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. • 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 CHADS2-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.
American College of Cardiology/American Heart Association: **Guideline for the Management of ST-Elevation Myocardial Infarction (2013)**[26]	Routine medical therapies: β-blockers • 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. Routine medical therapies: renin-angiotensin-aldosterone system inhibitors • An ACE inhibitor should be administered within the first 24 hours to all patients with ST-segment elevation myocardial infarction with anterior location, heart

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	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 (2012)**[27]	<u>Routine therapies in the acute, subacute and long term phase of STEMI</u> • Active smokers with STEMI must receive counseling and be referred to a smoking cessation program. • Each hospital participating in the care of STEMI patients must have a smoking cessation protocol. • Exercise-based rehabilitation is recommended. • Antiplatelet therapy with low dose aspirin (75 to 100 mg) is indicated indefinitely after STEMI. • In patients intolerant to aspirin, clopidogrel is indicated as an alternative. • Dual antiplatelet therapy with a combination of aspirin and prasugrel or aspirin and ticagrelor is recommended (over aspirin and clopidogrel) in patients treated with PCI. • Dual antiplatelet therapy with aspirin and an oral ADP receptor antagonist must be continued for up to 12 months after STEMI, with a strict minimum of 1 month for patients receiving bare metal stent and 6 months for patients receiving drug-eluting stent. • In patients with left ventricular thrombus, anticoagulation should be instituted for a minimum of 3 months. • In patients with a clear indication for oral anticoagulation (e.g. atrial fibrillation with CHA2DS2-VASc Score ≥2 or mechanical valve prosthesis), oral anticoagulation must be implemented in addition to antiplatelet therapy. • If patients require triple antithrombotic therapy, combining dual antiplatelet therapy and oral anticoagulant, e.g. because of stent placement and an obligatory indication for oral anticoagulation, the duration of dual antiplatelet therapy should be minimized to reduce bleeding risk. • 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 1 year in patients with STEMI who did not receive a stent. • Gastric protection with a proton pump inhibitor should be considered for the duration of DAPT therapy in patients at high risk of bleeding. • 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. • Intravenous β-blockers must be avoided in patients with hypotension or heart failure. • Intravenous β-blockers should be considered at the time of presentation in patients 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

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	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. • Reassessment of LDL-cholesterol should be considered after 4–6 weeks to ensure that a target value of ≤70 mg/dL has been reached. • Verapamil may be considered for secondary prevention in patients with absolute contraindications to β-blockers and no heart failure. • 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.

National Institute for Health and Clinical Excellence: **Myocardial Infarction: cardiac rehabilitation and prevention of further cardiovascular disease (2013)**[28]	Drug therapy
	• Offer all people who have had an acute MI treatment with the following drugs:
	  ○ ACE inhibitor
	  ○ Dual antiplatelet therapy (aspirin plus a second antiplatelet agent)
	  ○ β-blocker
	  ○ Statin
	
	Antiplatelet therapy
	• Offer aspirin to all people after an MI and continue indefinitely, unless they are aspirin intolerant or have an indication for anticoagulation.
	• Offer aspirin to people who have had an MI more than 12 months ago and continue it indefinitely.
	• For patients with aspirin hypersensitivity, clopidogrel monotherapy should be considered as an alternative treatment.
	• Special considerations should be made for people with dyspepsia.
	• After appropriate treatment, people with a history of aspirin-induced ulcer bleeding whose ulcers have healed and who are negative for Helicobacter pylori should be considered for treatment in line with dyspepsia.
	• Ticagrelor in combination with low-dose aspirin is recommended for up to 12 months as a treatment option in adults with ACS (STEMI, PCI, or NSTEMI).
	• Offer clopidogrel as a treatment option for up to 12 months to people who have had an NSTEMI, regardless of treatment, or people who have had a STEMI and received a bare-metal or drug-eluting stent.
	• Offer clopidogrel as a treatment option for at least one month and consider continuing for up to 12 months in people who have had a STEMI and medical management with or without reperfusion treatment with a fibrinolytic agent.
	• Continue the second antiplatelet agent for up to 12 months in people who have had a STEMI and who received CABG surgery.
	• Offer clopidogrel instead of aspirin to people who also have other clinical vascular disease (had an MI and stopped dual antiplatelet therapy or had an MI more than 12 months ago).
	
	Antiplatelet therapy in people with an indication for anticoagulation
	• Take bleeding risk, thromboembolic risk, and cardiovascular risk into account when deciding which people who have had an MI and have an indication for anticoagulation.

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	• Unless there is a high risk of bleeding, continue anticoagulation and add aspirin to treatment in people who have had an MI who otherwise need anticoagulation and who have had their condition managed medically or have undergone balloon angioplasty or have undergone CABG surgery. • Continue anticoagulation and add clopidogrel to treatment in people who have had an MI, who have undergone PCI with bare-metal or drug-eluting stents and who otherwise need anticoagulation. • Offer clopidogrel with warfarin to people with a sensitivity to aspirin who otherwise need anticoagulation and aspirin and who have had an MI. • Do not routinely offer warfarin in combination with prasugrel or ticagrelor to people who need anticoagulation who have had an MI. • After 12 months since the MI, continue anticoagulation and take into consideration the need for ongoing antiplatelet therapy, taking into account all of the following: indication for anticoagulation, thromboembolic risk, bleeding risk, cardiovascular risk and the person's wishes. • Do not add a new oral anticoagulant (rivaroxaban, apixaban or dabigatran) in combination with dual antiplatelet therapy in people who otherwise need anticoagulation, who have had an MI. • Consider using warfarin and discontinuing treatment with a new oral anticoagulant (rivaroxaban, apixaban, or dabigatran) in people who otherwise need anticoagulation and who have had an MI, unless there is a specific clinical indication to continue it.
American College of Cardiology/American Heart Association: **Guideline for the Management of Heart Failure (2013)**[29]	Treatment of Stage A heart failure (HF) • Hypertension and lipid disorders should be controlled in accordance with guidelines to lower the risk of HF. (Level of Evidence (LoE): A) • Other conditions that may lead to or contribute to HF, such as obesity, diabetes mellitus, tobacco use, and known cardiotoxic agents, should be controlled or avoided. (LoE: C) Treatment of Stage B heart failure • In patients with a history of MI and reduced EF, ACE inhibitors or ARBs should be used to prevent HF. (LoE: A) • In patients with MI and reduced EF, evidence-based β-blockers (using one of three proven to reduce mortality [i.e., bisoprolol, carvedilol, and sustained-release metoprolol succinate]) should be used to prevent HF. (LoE: B) • In patients with MI, statins should be used to prevent HF. (LoE: A) • ACE inhibitors and β-blockers should be used in all patients with a reduced EF to prevent symptomatic HF, even if they do not have a history of MI. (LoE: A and C, respectively) • Blood pressure should be controlled to prevent symptomatic HF. (LoE: A) • Nondihydropyridine calcium channel blockers may be harmful in patients with low LVEF. (LoE: C) Pharmacological treatment for Stage C HFrEF • Recommendations for patients in Stages A and B are recommended where appropriate for patients in Stage C. (LoE: A, B, and C as appropriate) • Diuretics are recommended in patients with HFrEF who have evidence of fluid retention, unless contraindicated, to improve symptoms. (LoE: C) • ACE inhibitors are recommended in patients with HFrEF and current or prior symptoms, unless contraindicated, to reduce morbidity and mortality. ARBs are recommended as alternative therapy in ACE inhibitor intolerant patients. (LoE: A) • Use of one of the three β-blockers proven to reduce mortality is recommended for all patients with current or prior symptoms of HFrEF, unless contraindicated, to reduce morbidity and mortality. (LoE: A)

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	• Aldosterone receptor antagonists are recommended in patients with NYHA class II–IV HF and who have LVEF of ≤35%, unless contraindicated, to reduce morbidity and mortality. Patients with NYHA class II HF should have a history of prior cardiovascular hospitalization or elevated plasma natriuretic peptide levels to be considered for aldosterone receptor antagonists. Creatinine should be ≤2.5 mg/dL in men or ≤2.0 mg/dL in women (or estimated glomerular filtration rate >30 mL/min/1.73 m^2), and potassium should be <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) • The combination of hydralazine and isosorbide dinitrate is recommended to reduce morbidity and mortality for patients self-described as African Americans with NYHA class III–IV HFrEF receiving optimal therapy with ACE inhibitors and β-blockers, unless contraindicated. (LoE: A) • Digoxin can be beneficial in patients with HFrEF, unless contraindicated, to decrease hospitalizations for HF. (LoE: B) • Patients with chronic HF with permanent/persistent/paroxysmal AF and an additional risk factor for cardioembolic stroke (history of hypertension, diabetes mellitus, previous stroke or transient ischemic attack, or ≥75 years of age) should receive chronic anticoagulant therapy. (LoE: A) • Statins are not beneficial as adjunctive therapy when prescribed solely for the diagnosis of HF in the absence of other indications for their use. (LoE: A) • Calcium channel blockers are not recommended as routine treatment for patients with HFrEF. (LoE: A) <u>Pharmacological treatment for Stage C HFpEF</u> • Blood pressure should be controlled according to published clinical practice guidelines. (LoE: B) • Diuretics should be used for relief of symptoms due to volume overload. (LoE: C) • The use of β-blocking agents, ACE inhibitors, and ARBs in patients with hypertension is reasonable to control blood pressure in patients with HFpEF. (LoE: C) <u>Treatment of Stage D (advanced/refractory) HF</u> • Fluid restriction (1.5 to 2 L/d) is reasonable, especially in patients with hyponatremia, to reduce congestive symptoms. (LoE: C) • Until definitive therapy (e.g., coronary revascularization, mechanical circulatory support, heart transplantation) or resolution of the acute precipitating problem, patients with cardiogenic shock should receive temporary intravenous inotropic support to maintain systemic perfusion and preserve end-organ performance. (LoE: C) • Continuous intravenous inotropic support is reasonable as "bridge therapy" in patients with stage D HF refractory to medical therapy and device therapy who are eligible for and awaiting mechanical circulatory support or cardiac transplantation. (LoE: B) • Long-term use of either continuous or intermittent, intravenous parenteral positive inotropic agents, in the absence of specific indications or for reasons other than palliative care, is potentially harmful in the patient with HF. (LoE: B)
Heart Failure Society of America: **Heart Failure Society of America 2010 Comprehensive Heart Failure**	<u>Patients with left ventricular systolic dysfunction</u> • ACE inhibitors should be used in all patients with a LVEF ≤40%, unless otherwise contraindicated. • ARBs may be used in patients who are intolerant to ACE inhibitors. Hydralazine and a nitrate may be used in patients intolerant to ACE inhibitors and ARBs, or in whom such therapy is contraindicated.

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Practice Guidelines (Executive Summary) (2010)[30]	• The combination of an ACE inhibitor and a β-blocker is recommended in all patients with a LVEF ≤40%. • The routine use of an ARB with a combination of an ACE inhibitor and β-blocker in patients who have had a MI and have left ventricular dysfunction is not recommended. • The addition of an ARB can be considered in patients with heart failure due to reduced LVEF who have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor and a β-blocker. • Individual ARBs may be considered as initial therapy (instead of an ACE inhibitor) in patients with heart failure who have had a MI and in patients with chronic heart failure and systolic dysfunction. • ARBs are recommended in patients who cannot tolerate ACE inhibitors due to cough. The combination of hydralazine and an oral nitrate may be considered in such patients not tolerating ARB therapy. • Patients intolerant to ACE inhibitors from hyperkalemia or renal insufficiency are likely to experience the same side effects with ARBs. In these cases, the combination of hydralazine and an oral nitrate should be considered. • ARBs should be considered in patients experiencing angioedema while on ACE inhibitors based on their underlying risk and with recognition that angioedema has been reported infrequently with ARBs. The combination of hydralazine and oral nitrates may be considered in such patients not tolerating ARB therapy. • A combination of hydralazine and an oral nitrate is recommended in African American patients with heart failure and reduced left ventricular ejection fraction (LVEF) who are on a standard regimen of an ACE inhibitor (or ARB) and a β-blocker. • A combination of hydralazine and an oral nitrate may be considered in non–African American patients with heart failure and reduced LVEF who are symptomatic despite optimization of standard therapy. • Administration of an aldosterone antagonist is recommended for patients with New York Heart Association (NYHA) class IV (or class III, previously class IV) heart failure from reduced LVEF (<35%) while receiving standard therapy, including diuretics. • Administration of an aldosterone antagonist should be considered in patients following an acute MI, with clinical heart failure signs and symptoms or history of diabetes mellitus, and an LVEF <40%. Patients should be on standard therapy, including an ACE inhibitor (or ARB) and a β-blocker. • The triple combination of an ACE inhibitor, an ARB, and an aldosterone antagonist is not recommended because of the high risk of hyperkalemia. <u>Patients with hypertension and symptomatic left ventricular dysfunction with left ventricular dilation and low LVEF</u> • ACE inhibitors, ARBs, β-blockers, aldosterone inhibitors, and isosorbide dinitrate/hydralazine in various combinations (with a loop diuretic if needed) are recommended. • If blood pressure remains >130/80 mm Hg, a dihydropyridine calcium channel blocker (e.g., amlodipine or felodipine) may be considered or other antihypertensive medication doses increased. <u>Managing heart failure in special populations</u> • The combination of hydralazine/isosorbide dinitrate is recommended for African American women with moderate to severe heart failure symptoms who are on background neurohormonal inhibition. • A combination of hydralazine and isosorbide dinitrate is recommended as part of standard therapy in addition to β-blockers and ACE-inhibitors for African Americans with left ventricular systolic dysfunction and NYHA class II-IV heart

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	failure. • As in all patients, but especially in the elderly, careful attention to volume status, the possibility of symptomatic cerebrovascular disease and the presence of postural hypotension are recommended during therapy with ACE inhibitors, β-blockers and diuretics. <u>Patients with heart failure and preserved LVEF</u> • ACE inhibitors or ARBs should be considered in this patient population. • ACE inhibitors should be considered in patients with heart failure and symptomatic atherosclerotic cardiovascular disease or diabetes and at least one other risk factor. ARBs may be used in patients who are intolerant to ACE inhibitors. • Beta-blocker treatment is recommended in patients with HF and preserved LVEF who have prior MI, hypertension, or AF. • Calcium channel blockers should be considered in patients with heart failure and preserved LVEF who have atrial fibrillation requiring ventricular rate control and intolerance to β-blockers (consider diltiazem or verapamil), symptom-limiting angina, or hypertension. • Diuretic therapy is recommended in all patients with heart failure and clinical evidence of volume overload, including those with preserved LVEF. • Treatment may begin with either a thiazide or loop diuretic. In more severe volume overload or if response to a thiazide is inadequate, treatment with a loop diuretic should be implemented. • Excessive diuresis, which may lead to orthostatic changes in blood pressure and worsening renal function, should be avoided. <u>Patients with heart failure and CAD</u> • Calcium channel blockers should be considered in patients who have angina despite optimization of β-blocker and nitrates. Amlodipine and felodipine are preferred in patients with decreased systolic function. <u>Patients with heart failure and hypertension</u> • Patients with left ventricular hypertrophy or left ventricular dysfunction without left ventricular dilation should be treated to a goal blood pressure of <130/80 mm Hg. Treatment with several drugs may be necessary, including an ACE inhibitor (or ARB), a diuretic and a β-blocker or calcium channel blocker. • Patients with asymptomatic left ventricular dysfunction and left ventricular dilation and a reduced ejection fraction should receive an ACE inhibitor and a β-blocker. If blood pressure remains elevated (>130/80 mm Hg), the addition of a diuretic is recommended, followed by a calcium channel blocker or other antihypertensive agent. • If blood pressure remains >130/80 mm Hg, then the addition of a thiazide diuretic is recommended, followed by a dihydropyridine calcium channel blocker (e.g., amlodipine or felodipine) or other antihypertensive drugs. <u>Patients at risk for development of heart failure</u> • ACE inhibitors are recommended in patients who are at risk for the development of heart failure including patients with CAD, peripheral vascular disease, stroke, diabetes and another major risk factor, and patients with diabetes who smoke and have microalbuminuria. <u>Patients with asymptomatic heart failure and reduced LVEF</u> • ACE inhibitors are recommended in asymptomatic patients with reduced LVEF (<40%). • ARBs may be used in patients who are intolerant to ACE inhibitors.

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	• Routine use of a combination of ACE inhibitors and ARBs is not recommended. • β-blocker therapy should be considered. <u>Patients with heart failure and ischemic heart disease</u> • ACE inhibitor therapy is recommended in all patients with either reduced or preserved LVEF after a MI. • Beta-blockers are recommended for the management of all patients with reduced LVEF or post-MI. • ACE inhibitor and β-blocker therapy should be initiated early (<48 hours) during hospitalization in hemodynamically stable patients who are post-MI with reduced LVEF or heart failure. • Calcium channel blockers may be considered in patients with HF who have angina despite the optimal use of β-blockers and nitrates. <u>Managing heart failure in the elderly, women and African Americans</u> • Standard regimens of ACE inhibitors and β-blockers are recommended in elderly patients with heart failure. • ACE inhibitor and β-blocker therapy are recommended in all women with heart failure and left ventricular systolic dysfunction. • ACE inhibitor and β-blocker therapy are recommended in all African American patients with heart failure and left ventricular systolic dysfunction. ARBs may be substituted in patients who are intolerant to ACE inhibitors. <u>Heart failure in patients with reduced ejection fraction</u> • ACE inhibitors are recommended in asymptomatic patients with reduced LVEF (<40%). • ARBs may be used in patients who are intolerant to ACE inhibitors. • β-blockers shown to be effective in clinical trials of patients with heart failure are recommended for patients with a LVEF ≤40%. • The combination of a β-blocker and an ACE inhibitor is recommended as routine therapy for asymptomatic patients with a LVEF ≤40%. The evidence is stronger in patients with a history of MI. • β-blocker therapy is recommended for patients with a recent decompensation of heart failure after optimization of volume status and successful discontinuation of intravenous diuretics and vasoactive drugs. Whenever possible, β-blocker therapy should be initiated in the hospital setting at a low dose prior to discharge of stable patients. • β-blocker therapy is recommended in the great majority of patients with heart failure and reduced LVEF, even if there is concurrent diabetes, chronic obstructive pulmonary disease or peripheral vascular disease. Caution may be warranted in these patients. • It is recommended that β blockade be initiated at low doses and uptitrated gradually. • It is recommended that β-blocker therapy be continued in most patients experiencing a symptomatic exacerbation of heart failure during chronic maintenance treatment, unless they develop cardiogenic shock, refractory volume overload or symptomatic bradycardia. • The routine use of an ARB is not recommended in addition to an ACE inhibitor and a β-blocker in patients with a recent acute MI and reduced LVEF. • The addition of an ARB should be considered in patients with heart failure due to reduced LVEF who have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor and a β-blocker. • Administration of an aldosterone antagonist is recommended for patients with NYHA class IV (or class III, previously class IV) HF from reduced LVEF (<35%) while receiving standard therapy, including diuretics.

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	• Diuretic therapy is recommended to restore and maintain normal volume status in patients with clinical evidence of fluid overload, generally manifested by congestive symptoms or signs of elevated filling pressures. Loop diuretics rather than thiazide-type diuretics are typically necessary to restore normal volume status in patients with heart failure. • The initial dose of diuretic may be increased as necessary to relieve congestion, and restoration of normal volume status may require multiple adjustments, especially in patients with severe fluid overload evidenced by massive edema or ascites. After a diuretic effect is achieved with loop diuretics (short acting), increasing administration frequency to twice or even three times/day will provide more diuresis with less physiologic perturbation than larger single doses. • Oral torsemide may be considered in patients in whom poor absorption of oral medication or erratic diuretic effect may be present. Particularly in patients with right-sided heart failure and refractory fluid retention despite high doses of other loop diuretics. • Intravenous administration of diuretics may be necessary to relieve congestion. • Diuretic refractoriness may represent patient nonadherence, a direct effect of diuretic use on the kidney or progression of underlying cardiac dysfunction. • Addition of chlorothiazide or metolazone, once or twice daily, to loop diuretics should be considered in patients with persistent fluid retention despite high dose loop diuretic therapy. Chronic daily use should be avoided if possible because of the potential for electrolyte shifts and volume depletion. These drugs may be used periodically (every other day or weekly) to optimize fluid management. Metolazone will generally be more potent and much longer acting in this setting and in patients with chronic renal insufficiency, so administration should be adjusted accordingly. Volume status and electrolytes must be monitored closely when multiple diuretics are used. • Careful observation for the development of side effects is recommended in patients treated with diuretics, especially when high doses or combination therapy are used. Patients should undergo routine laboratory studies and clinical examination as dictated by their clinical response. • Patients requiring diuretic therapy to treated fluid retention associated with heart failure generally require chronic treatment, although often at lower doses than those required initially to achieve diuresis. Decreasing or discontinuing therapy may be considered in patients experiencing significant improvement in clinical status and cardiac function or in those who successfully restrict dietary sodium intake. These patients may undergo cautious weaning of diuretic dose and frequency with careful observation for recurrent fluid retention. • Patients and caregivers should be given education on the early signs of fluid retention and the plan for initial therapy. • Selected patients may be educated to adjust daily dose of diuretic in response to weight gain from fluid overload. <u>Evaluation and management of patients with acute decompensated heart failure</u> • Patients admitted with acute decompensated heart failure and evidence of fluid overload be treated initially with loop diuretics; usually given intravenously rather than orally. Ultrafiltration may be considered in lieu of diuretics. • Diuretics should be administered at doses needed to produce a rate of diuresis sufficient to achieve optimal volume status with relief of signs and symptoms of congestion, without inducing an excessively rapid reduction in intravascular volume or serum electrolytes. • Monitoring of daily weights, intake and output is recommended to assess clinical efficacy of diuretic therapy. • Careful observation for development of a variety of side effects, including renal dysfunction, electrolyte abnormalities, symptomatic hypotension and gout is

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	recommended in patients treated with diuretics, especially when high doses or combination therapy is used.
	• Careful observation for the development of renal dysfunction is recommended in patients treated with diuretics. Patients with moderate to severe renal dysfunction and evidence of fluid retention should continue to be treated with diuretics. In the presence of severe fluid overload, renal dysfunction may improve with diuresis.
	• When congestion fails to improve in response to diuretic therapy, the following options should be considered:
	  ○ Re-evaluating the presence/absence of congestion.
	  ○ Sodium and fluid restriction.
	  ○ Increasing doses of loop diuretic.
	  ○ Continuous infusion of a loop diuretic.
	  ○ Addition of a second type of diuretic orally (metolazone or spironolactone) or intravenously (chlorothiazide).
	  ○ Ultrafiltration may be considered as well.

European Society of Cardiology: **Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (2016)**[31]	Pharmacological treatments indicated in patients with symptomatic (NYHA Class II-IV) heart failure with reduced ejection fraction • An ACE inhibitor is recommended, in addition to a beat-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death. • A mineralocorticoid receptor antagonist 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. • Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion. • 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. • 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. • 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

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	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). Recommendations for treatment of patients with heart failure with preserved ejection fraction and heart failure with mid-range ejection fraction • It is recommended to screen patients with HFpEF or HFmrEF (mid-range) 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 or HFmrEF in order to alleviate symptoms and signs. Recommendations for initial management of a rapid ventricular rate in patients with heart failure and atrial fibrillation in the acute or chronic setting • Urgent electrical cardioversion is recommended if AF is thought to be contributing to the patient's hemodynamic compromise in order to improve the patient clinical condition. • For patients in NYHA Class IV, in addition to treatment for acute HF, an intravenous bolus of amiodarone or, in digoxin-naïve patients, an intravenous bolus of digoxin should be considered to reduce the ventricular rate. • For patients in NYHA Class I–III, a β-blocker, usually given orally, is safe and therefore is recommended as first-line treatment to control ventricular rate, provided the patient is euvolemic. • For patients in NYHA Class I–III, digoxin should be considered when ventricular rate remains high despite β-blockers or when β-blockers are not tolerated or contraindicated. • Treatment with dronedarone to improve ventricular rate control is not recommended due to safety concerns. Recommendations for cardiac imaging in patients with suspected or established heart failure • Transthoracic Echocardiogram (TTE) is recommended for the assessment of myocardial structure and function in subjects with suspected HF in order to establish a diagnosis of HFrEF, HFmrEF, or HFpEF. • TTE is recommended for the assessment of LVEF in order to identify patients with HF who would be suitable for evidence-based pharmacological and device treatment recommended for HFrEF. Recommendations aiming to prevent or delay the development of overt heart failure or prevent death before the onset of symptoms • Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life. • ACE inhibitor is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction in order to prevent or delay the onset of HF and prolong life. • Beta-blocker is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction, in order to prevent or delay the onset of HF and prolong life. Pharmacological treatments indicated in patients with symptomatic 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 β-blocker is recommended, in addition to an ACE inhibitor, for patients with

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	stable, symptomatic HFrEF to reduce the risk of HF hospitalization and death. • A mineralocorticoid receptor antagonist 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. Other pharmacological treatments recommended in selected patients with symptomatic heart failure with reduced ejection fraction • Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion. • 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. Treatments (or combinations of treatments) that may cause harm in patients with symptomatic (New York Heart Association Class II–IV) heart failure with reduced ejection fraction • Diltiazem or verapamil are not recommended in patients with HFrEF, as they increase the risk of HF worsening and HF hospitalization. • The addition of an ARB (or a renin inhibitor) to the combination of an ACE inhibitor and a mineralocorticoid receptor antagonist is not recommended in patients with HF, because of the increased risk of renal dysfunction and hyperkalemia. Not-recommended treatments of co-morbidities in patients with heart failure • Thiazolidinediones (glitazones) are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization. • NSAIDs or COX-2 inhibitors are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization. Recommendations for the 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. • In patients with new-onset AHF or those with chronic, decompensated HF not receiving oral diuretics the initial recommended dose should be 20 to 40 mg intravenous furosemide (or equivalent); for those on chronic diuretic therapy, initial intravenous dose should be at least equivalent to oral dose. • It is recommended to give diuretics either as intermittent boluses or a continuous infusion, and the dose and duration should be adjusted according to the patients' symptoms and clinical status. • Inotropic agents are not recommended unless the patient is symptomatically hypotensive or hypoperfused because of safety concern.
Eighth Joint National Committee (JNC 8): **2014 Evidence-based Guideline for the Management of High Blood Pressure in Adults (2014)**[32]	• 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.

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	• 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.
American Society of Hypertension/ International Society of Hypertension: **Clinical Practice Guidelines for the Management of Hypertension in the Community (2014)**[33]	Nonpharmacologic treatment • In patients with hypertension that is no more severe than stage one and is not associated with evidence of abnormal cardiovascular findings or other cardiovascular risks, six to 12 months of lifestyle changes can be attempted in the hope that they may be sufficiently effective to make it unnecessary to use medicines. • It may be prudent to start treatment with drugs sooner if it is clear that the blood pressure is not responding to the lifestyle methods or if other risk factors appear. • Weight loss: In patients who are overweight or obese, weight loss is helpful in treating hypertension, diabetes, and lipid disorders. • Salt reduction: Reduction of salt intake is recommended because it can reduce blood pressure and decrease the need for medications in patients who are "salt sensitive." • Exercise: Regular aerobic exercise can help reduce blood pressure. • Alcohol consumption: Up to two drinks a day can be helpful in protecting against cardiovascular events, but greater amounts of alcohol can raise blood pressure and should therefore be discouraged. In women, alcohol should be limited to one drink a day. • Cigarette smoking: Stopping smoking will not reduce blood pressure, but since smoking by itself is such a major cardiovascular risk factor, patients must be strongly urged to discontinue this habit. Drug treatment of hypertension • Treatment with drugs should be started in patients with blood pressures >140/90 mm Hg in whom lifestyle treatments have not been effective. • In patients with stage two hypertension (blood pressure ≥160/100 mm Hg), drug treatment should be started immediately after diagnosis, usually with a two-drug

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	combination, without waiting to see the effects of lifestyle changes.
	• For patients older than 80 years, the suggested threshold for starting treatment is at levels ≥150/90 mm Hg. Thus, the target of treatment should be <140/90 mm Hg for most patients but <150/90 mm Hg for older patients (unless these patients have chronic kidney disease or diabetes, when <140/90 mm Hg can be considered).
	• Most patients will require more than one drug to achieve control of their blood pressure.
	• In general, increase the dose of drugs or add new drugs at approximately two to three week intervals. This frequency can be faster or slower depending on the judgment of the practitioner. In general, the initial doses of drugs chosen should be at least half of the maximum dose so that only one dose adjustment is required thereafter. It is generally anticipated that most patients should reach an effective treatment regimen, whether one, two, or three drugs, within six to eight weeks.
	• Choice of drugs should be influenced by the age, ethnicity/race, and other clinical characteristics of the patient.
	• The choice of drugs will also be influenced by other conditions (e.g., diabetes and coronary disease) associated with the hypertension. Pregnancy also influences drug choice.
	• Long-acting drugs that need to be taken only once daily are preferred to shorter-acting drugs that require multiple doses because patients are more likely to follow a simple treatment regimen.
	• This guideline only makes recommendations for drug classes, not individual agents. There is an assumption, unless otherwise stated, that all drugs in a class are similar to each other.
	• Drug selectin when hypertension is the only or main concern:
	  ○ For black patients of all ages, use calcium channel blocker (CCB) or thiazide diuretic as first drug, then add angiotensin receptor blocker (ARB) or angiotensin-converting enzyme (ACE) inhibitor if needed.
	  ○ For white and other non-black patients <60 years of age, use ARB or ACE inhibitor as first drug, then add CCB or thiazide diuretic if needed.
	  ○ For white and other non-black patients ≥60 years of age, use CCB or thiazide diuretic as first drug, then add ARB or ACE inhibitor if needed.
	• Drug selection when hypertension is associated with other conditions:
	  ○ For patients with hypertension and diabetes, use ARB or ACE inhibitor as first drug (note, in black patients it is acceptable to start with a CCB or thiazide), then add CCB or thiazide diuretic (unless starting on CCB or thiazide in black patients) if needed.
	  ○ For patients with hypertension and chronic kidney disease, use ARB or ACE inhibitor as first drug, then add CCB or thiazide diuretic if needed.
	  ○ For patients with hypertension and clinical coronary artery disease, use β-blocker plus ARB or ACE inhibitor as first drugs, then add CCB or thiazide diuretic if needed.
	  ○ For patients with hypertension and stroke history, use ACE inhibitor or ARB as first drug, then add thiazide diuretic or CCB if needed.
	• For patients with hypertension and heart failure, patients with h symptomatic heart failure should usually receive an ARB or ACE inhibitor plus β-blocker plus diuretic plus spironolactone regardless of blood pressure. A dihydropyridine CCB can be added if needed for blood pressure control.

Hypertension Canada: **2017 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of**	<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.

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Hypertension in Adults (2017)[34]	• 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.
	
	<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>Guidelines for individuals 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.

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	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. Treatment of hypertension in association with stroke • BP management in acute ischemic stroke (onset to 72 hours) ○ For patients with ischemic stroke not eligible for thrombolytic therapy, treatment of hypertension in the setting of acute ischemic stroke or transient ischemic attack should not be routinely undertaken. Extreme BP increases (e.g., SBP >220 mmHg or DBP >120 mmHg) may be treated to reduce the

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	BP by approximately 15%, and not more than 25%, over the first 24 hours with gradual reduction thereafter. Avoid excessive lowering of BP because this might exacerbate existing ischemia or might induce ischemia, particularly in the setting of intracranial arterial occlusion or extracranial carotid or vertebral artery occlusion. Pharmacological agents and routes of administration should be chosen to avoid precipitous decreases in BP. ○ For patients with ischemic stroke eligible for thrombolytic therapy, very high BP (>185/110 mmHg) should be treated concurrently in patients receiving thrombolytic therapy for acute ischemic stroke to reduce the risk of secondary intracranial hemorrhage. • 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) ○ For patients with intracerebral hemorrhage (ICH) in the hyperacute phase (in the first 24 hours) SBP lowering to <140 mmHg should be avoided because of an absence of benefit (relative to a target of <180 mmHg) and some suggestion of harm. <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> • For patients with nondiabetic chronic kidney disease, target BP is <140/90 mmHg. • For patients with hypertension and proteinuric chronic kidney disease (urinary protein >500 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. • Thiazide/thiazide-like diuretics are recommended as additive antihypertensive therapy. For patients with chronic kidney disease and volume overload, loop diuretics are an alternative. • 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.

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	• Patients with confirmed renal fibromuscular dysplasia (FMD) should be referred to a hypertension specialist. • In patients with hypertension attributable to FMD-related renal artery stenosis, revascularization should be considered. • 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 2 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. Combination therapy using two first-line agents may also be considered as initial treatment of hypertension if SBP is 20 mmHg greater than target or if DBP is 10 mmHg greater than target. However, caution should be exercised in patients in whom a substantial decrease in BP is more likely or poorly tolerated (e.g., elderly patients and patients with autonomic neuropathy). • 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.
European Society of Hypertension/ European Society of Cardiology: **2013 Guidelines for the management of arterial hypertension (2013)**[35]	The 2013 guidelines on hypertension of the European Society of Hypertension and the European Society of Cardiology follow the guidelines jointly issued by the two societies in 2003 and 2007. <u>Treatment strategies and choice of antihypertensive drugs</u> • Diuretics (including thiazides, chlorthalidone, and indapamide), β-blockers, calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) are all suitable for the initiation and maintenance of antihypertensive treatment, either as monotherapy or in some combinations. • Some agents should be considered as the preferential choice in specific conditions because used in trials in those conditions or because of greater effectiveness in specific types of organ damage. • Initiation of antihypertensive therapy with a two-drug combination may be considered in patients with markedly high baseline blood pressure (BP) or at high cardiovascular (CV) risk. • The combination of two antagonists of the renin-angiotensin system (RAS) is not recommended and should be discouraged. • Other drug combinations should be considered and probably are beneficial in proportion to the extent of BP reduction. However, combinations that have been successfully used in trials may be preferable. • Combinations of two antihypertensive drugs at fixed doses in a single tablet may be recommended and favored, because reducing the number of daily pills improves adherence, which is low in patients with hypertension. <u>Treatment strategies in white-coat and masked hypertension</u> • In white-coat hypertensives without additional risk factors, therapeutic intervention may be limited to lifestyle changes only, but this decision should be

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	accompanied by close follow-up. • In white-coat hypertensives with a higher CV risk because of metabolic derangements or asymptomatic organ damage, drug treatment may be considered in addition to lifestyle changes. • In masked hypertension, both lifestyle measures and antihypertensive drug treatment should be considered, because this type of hypertension has been consistently found to have a CV risk very close to that of in- and out-of-office hypertension. <u>Antihypertensive treatment strategies in the elderly</u> • In elderly hypertensives with SBP ≥160 mmHg there is solid evidence to recommend reducing SBP to between 150 and 140 mmHg. • In fit elderly patients <80 years old antihypertensive treatment may be considered at SBP values ≥140 mmHg with a target SBP <140 mmHg if treatment is well tolerated. • In individuals older than 80 years with an initial SBP ≥160 mmHg, it is recommended to reduce SBP to between 150 and 140 mmHg, provided they are in good physical and mental conditions. • In frail elderly patients, it is recommended to leave decisions on antihypertensive therapy to the treating physician, and based on monitoring of the clinical effects of treatment. • Continuation of well-tolerated antihypertensive treatment should be considered when a treated individual becomes an octogenarian. • All hypertensive agents are recommended and can be used in the elderly, although diuretics and calcium antagonists may be preferred in isolated systolic hypertension. <u>Treatment strategies in hypertensive women</u> • Hormone therapy and selective estrogen receptor modulators are not recommended and should not be used for primary or secondary prevention of CVD. • If treatment of younger perimenopausal women is considered for severe menopausal symptoms, the benefits should be weighed against potential risks. • Drug treatment of severe hypertension in pregnancy (SBP >160 mmHg or DBP >110 mmHg) is recommended. • Drug treatment may also be considered in pregnant women with persistent elevation of BP ≥150/95 mmHg, and in those with BP ≥140/90 mmHg in the presence of gestational hypertension, subclinical organ damage or symptoms. • In women at high risk of pre-eclampsia, provided they are at low risk of gastrointestinal hemorrhage, treatment with low dose aspirin from 12 weeks until delivery may be considered. • In women with child-bearing potential RAS blockers are not recommended and should be avoided. • Methyldopa, labetalol, and nifedipine should be considered preferential antihypertensive drugs in pregnancy. Intravenous labetalol or infusion of nitroprusside should be considered in case of emergency (pre-eclampsia). <u>Treatment strategies in patients with diabetes</u> • While initiation of antihypertensive drug treatment in diabetic patients whose SBP is ≥160 mmHg is mandatory, it is strongly recommended to start drug treatment also when SBP is ≥140 mmHg. • A SBP goal <140 mmHg is recommended in patients with diabetes. • The DBP target in patients with diabetes is recommended to be <85 mmHg. • All classes of antihypertensive agents are recommended and can be used in patients with diabetes; RAS blockers may be preferred, especially in the presence

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	of proteinuria or microalbuminuria. • It is recommended that individual drug choice takes comorbidities into account. • Simultaneous administration of two blockers of the RAS is not recommended and should be avoided in patients with diabetes <u>Treatment strategies in hypertensive patients with metabolic syndrome</u> • Lifestyle changes, particularly weight loss and physical exercise, are to be recommended to all individuals with the metabolic syndrome. These interventions improve not only BP, but the metabolic components of the syndrome and delay diabetes onset. • As the metabolic syndrome can be considered a 'pre-diabetic' state, antihypertensive agents potentially improving or at least not worsening insulin sensitivity, such as RAS blockers and calcium antagonists, should be considered as the preferred drugs. Beta-blockers (with the exception of vasodilating β-blockers) and diuretics should be considered only as additional drugs, preferably in association with a potassium-sparing agent. • It is recommended to prescribe antihypertensive drugs with particular care in hypertensive patients with metabolic disturbances when BP is ≥140/90 mmHg after a suitable period of lifestyle changes, and to maintain BP <140/90 mmHg. • BP lowering drugs are not recommended in individuals with metabolic syndrome and high normal BP. <u>Therapeutic strategies in hypertensive patients with nephropathy</u> • Lowering SBP to <140 mmHg should be considered. • When overt proteinuria is present, SBP values <130 mmHg may be considered, provided that changes in eGFR are monitored. • RAS blockers are more effective in reducing albuminuria than other antihypertensive agents, and are indicated in hypertensive patients in the presence of microalbuminuria or overt proteinuria. • Reaching BP goals usually requires combination therapy, and it is recommended to combine RAS blockers with other antihypertensive agents. • Combination of two RAS blockers, though potentially more effective in reducing proteinuria, is not recommended. • Aldosterone antagonists cannot be recommended in chronic kidney disease (CKD), especially in combination with a RAS blocker, because of the risk of excessive reduction in renal function and of hyperkalemia. <u>Therapeutic strategies in hypertensive patients with cerebrovascular disease</u> • It is not recommended to intervene with BP-lowering therapy during the first week after acute stroke irrespective of BP level, although clinical judgement should be used in the face of very high SBP values. • Antihypertensive treatment is recommended in hypertensive patients with a history of stroke or transient ischemic attack (TIA), even when initial SBP is in the 140 to 159 mmHg range. • In hypertensive patients with a history of stroke or TIA, a SBP goal of <140 mmHg should be considered. • In elderly hypertensives with previous stroke or TIA, SBP values for intervention and goal may be considered to be somewhat higher. • All drug regimens are recommended for stroke prevention, provided that BP is effectively reduced. <u>Therapeutic strategies in hypertensive patients with heart disease</u> • In hypertensive patients with CHD, a SBP goal <140 mmHg should be considered. • In hypertensive patients with a recent myocardial infarction, β-blockers are

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	recommended. In case of other CHD all antihypertensive agents can be used, but β-blockers and calcium antagonists are to be preferred for symptomatic reasons (angina). • Diuretics, β-blockers, ACE inhibitors, angiotensin receptor blockers, and/or mineralocorticoid receptor antagonists are recommended in patients with heart failure or severe left ventricular (LV) dysfunction to reduce mortality and hospitalization. • In patients with heart failure and preserved ejection fraction (EF), there is no evidence that antihypertensive therapy per se or any particular drug is beneficial. However, in these patients, as well as in patients with hypertension and systolic dysfunction, lowering SBP to around 140 mmHg should be considered. Treatment guided by relief of symptoms (congestion with diuretics, high heart rate with β-blockers, etc.) should also be considered. • ACE inhibitors and angiotensin receptor blockers (and β-blockers and mineralocorticoid receptor antagonists if heart failure coexists) should be considered as antihypertensive agents in patients at risk of new or recurrent atrial fibrillation. • It is recommended that all patients with left ventricular hypertrophy (LVH) receive antihypertensive agents. • In patients with LVH, initiation of treatment with one of the agents that have shown a greater ability to regress LVH should be considered, i.e. ACE inhibitors, angiotensin receptor blockers, and calcium antagonists. Therapeutic strategies in hypertensive patients with atherosclerosis, arteriosclerosis, and peripheral artery disease (PAD) • In the presence of carotid atherosclerosis, prescription of calcium antagonists and ACE inhibitors should be considered as these agents have shown a greater efficacy in delaying atherosclerosis progression than diuretics and β-blockers. • In hypertensive patients with a pulse wave velocity above 10 m/s, all antihypertensive drugs should be considered provided that a BP reduction to <140/90 mmHg is consistently achieved. • Antihypertensive therapy is recommended in hypertensive patients with PAD to achieve a goal of <140/90 mmHg, because of their high risk of myocardial infarction, stroke, heart failure, and CV death. • Though a careful follow up is necessary, β-blockers may be considered for the treatment of arterial hypertension in patients with PAD, since their use does not appear to be associated with exacerbation of PAD symptoms.
National Institute for Health and Clinical Excellence: **Hypertension in adults: diagnosis and management (2011)**[36] **Reaffirmed Nov 2016**	Choosing antihypertensive drug treatment • 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 people ≥80 years of age the same antihypertensive drug treatment as people aged 55 to 80 years, taking into account any comorbidities. • Offer antihypertensive drug treatment to women of child-bearing potential in line with the recommendations on Management of pregnancy with chronic hypertension and Breastfeeding in 'Hypertension in pregnancy' (NICE clinical guideline 107). 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). If an ACE inhibitor is not tolerated, offer an ARB. • Do not combine an ACE inhibitor with an ARB for the treatment of

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	hypertension.
	• Offer a step one antihypertensive (ACE inhibitor, ARB) with a calcium channel blocker (CCB) to patients >55 years of age and to black patients of African or Caribbean family origin 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 chlorthalidone (12.5 to 25.0 mg once daily) or indapamide (1.5 mg modified-release once daily or 2.5 mg once daily) in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide.
	• For patients who are already receiving treatment with bendroflumethiazide or hydrochlorothiazide and whose blood pressure is stable and well controlled, continue treatment as is.
	• β-blockers are not a preferred initial therapy for hypertension; however, β-blockers may be considered in younger patients, particularly:
	  ○ Patients with an intolerance or contraindication to ACE inhibitors and ARBs.
	  ○ Women of child-bearing potential.
	  ○ People with evidence of increased sympathetic drive.
	• If treatment is initiated with a β-blocker and a second antihypertensive is required, add a CCB over a thiazide-like diuretic to reduce the risk of developing diabetes.
	
	<u>Step two treatment</u>
	• If blood pressure is not controlled with a step one antihypertensive, offer a step two treatment with a CCB in combination with an ACE inhibitor or an ARB.
	• If a CCB is not appropriate or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic.
	• For black patients of African or Caribbean family origin, consider an ARB in preference to an ACE inhibitor, in combination with a CCB.
	
	<u>Step three treatment</u>
	• Before considering step three treatment, review medication to ensure step two treatment is at optimal or best tolerated doses.
	• If three drugs are required to control blood pressure, the combination of an ACE inhibitor or ARB, CCB, and thiazide-like diuretic should be utilized.
	
	<u>Step four treatment</u>
	• Regard clinic blood pressure that remains >140/90 mmHg after treatment with the optimal or best tolerated doses of an ACE inhibitor or an ARB plus a CCB plus a diuretic as resistant hypertension, and consider adding a fourth antihypertensive drug and/or seeking expert advice.
	• For treatment of resistant hypertension at step four:
	  ○ Consider further diuretic therapy with low-dose spironolactone (25 mg once daily) if the blood potassium level is 4.5 mmol/l or lower. Use particular caution in people with a reduced estimated glomerular filtration rate because they have an increased risk of hyperkalemia.
	  ○ Consider higher-dose thiazide-like diuretic treatment if the blood potassium level is higher than 4.5 mmol/l.
	  ○ If further diuretic therapy for resistant hypertension is not tolerated or is contraindicated or ineffective, consider an α-blocker or β-blocker.

International Society on Hypertension in Blacks: **Management of High**	• 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.

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Blood Pressure in Blacks (2010)[37]	• 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 (2012)[38]**	<u>Blood pressure management in chronic kidney disease (CKD) non-dialysis (ND) patients without diabetes mellitus</u> • The Work Group recommends that non-diabetic adults with CKD ND and urine albumin excretion <30 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >140 mm Hg systolic or >90 mm Hg diastolic be treated with blood pressure -lowering drugs to maintain a blood pressure that is consistently ≤140 mm Hg systolic and ≤90 mm Hg diastolic. • The Work Group suggests that non-diabetic adults with CKD ND and urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with BP-lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic. • The Work Group suggests that non-diabetic adults with CKD ND and urine albumin excretion >300 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with blood pressure -lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤ 80 mm Hg diastolic. • The Work Group suggests that an angiotensin receptor blocker (ARB) or angiotensin converting enzyme inhibitor (ACE-I) be used in non-diabetic adults with CKD ND and urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*) in whom treatment with blood pressure -lowering drugs is indicated. • The Work Group recommends that an ARB or ACE-I be used in non-diabetic adults with CKD ND and urine albumin excretion >300 mg per 24 hours (or equivalent*) in whom treatment with blood pressure -lowering drugs is indicated. <u>Blood pressure management in CKD ND patients with diabetes mellitus</u> • The Work Group recommends that adults with diabetes and CKD ND with urine albumin excretion <30 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >140 mm Hg systolic or >90 mm Hg diastolic be treated with BP-lowering drugs to maintain a blood pressure that is consistently ≤140 mm Hg systolic and ≤90 mm Hg diastolic. • The Work Group suggests that adults with diabetes and CKD ND with urine albumin excretion >30 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with BP-lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic.

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	• The Work Group suggests that an ARB or ACE-I be used in adults with diabetes and CKD ND with urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*). • The Work Group recommends that an ARB or ACE-I be used in adults with diabetes and CKD ND with urine albumin excretion >300 mg per 24 hours (or equivalent*). Blood pressure management in kidney transplant recipients (non–dialysis-dependent CKD of any stage with a kidney transplant [CKD T]) • The Work Group suggests that adult kidney transplant recipients whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic, irrespective of the level of urine albumin excretion. • In adult kidney transplant recipients, choose a blood pressure -lowering agent after taking into account the time after transplantation, use of calcineurin inhibitors, presence or absence of persistent albuminuria, and other co morbid conditions. Blood pressure management in children with CKD ND • The Work Group recommends that in children with CKD ND, blood pressure -lowering treatment is started when blood pressure is consistently above the 90th percentile for age, sex, and height. • The Work Group suggests that in children with CKD ND (particularly those with proteinuria), blood pressure is lowered to consistently achieve systolic and diastolic readings less than or equal to the 50th percentile for age, sex, and height, unless achieving these targets is limited by signs or symptoms of hypotension. • The Work Group suggests that an ARB or ACE-I be used in children with CKD ND in whom treatment with blood pressure -lowering drugs is indicated, irrespective of the level of proteinuria. Blood pressure management in elderly persons with CKD ND • Tailor blood pressure treatment regimens in elderly patients with CKD ND by carefully considering age, co-morbidities and other therapies, with gradual escalation of treatment and close attention to adverse events related to blood pressure treatment, including electrolyte disorders, acute deterioration in kidney function, orthostatic hypotension and drug side effects. *Approximate equivalents for albumin excretion rate per 24 hours is expressed as protein excretion rate per 24 hours, albumin/creatinine ratio, protein/creatinine ratio, and protein reagent strip results.
American Diabetes Association: **Standards of Medical Care in Diabetes (2017)**[39]	Hypertension/blood pressure control • Blood pressure should be measured at every routine visit. Patients found to have elevated blood pressure should have blood pressure confirmed on a separate day. • Most patients with diabetes and hypertension should be treated to a systolic blood pressure goal of <140 mmHg and a diastolic blood pressure goal of <90 mmHg. • Lower systolic and diastolic blood pressure targets, such as 130/80 mmHg, may be appropriate for individuals at high risk of cardiovascular disease, if they can be achieved without undue treatment burden. • In pregnant patients with diabetes and chronic hypertension, blood pressure targets of 120 to 160/80 to 105 mmHg are suggested in the interest of optimizing long-term maternal health and minimizing impaired fetal growth. • Patients with confirmed office-based blood pressure >140/90 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of pharmacologic therapy to achieve blood pressure goals.

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	• 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). 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. • For patients with blood pressure >120/80 mmHg, lifestyle intervention consists of weight loss if overweight or obese; a Dietary Approaches to Stop Hypertension–style dietary pattern including reducing sodium and increasing potassium intake; moderation of alcohol intake; and increased physical activity. <u>Coronary heart disease</u> • In asymptomatic patients, routine screening for coronary artery disease is not recommended as it does not improve outcomes as long as atherosclerotic cardiovascular disease risk factors are treated. • Consider investigations for coronary artery disease in the presence of any of the following: atypical cardiac symptoms (e.g., unexplained dyspnea, chest discomfort); signs or symptoms of associated vascular disease including carotid bruits, transient ischemic attack, stroke, claudication, or peripheral arterial disease; or electrocardiogram abnormalities (e.g., Q waves). • In patients with known atherosclerotic cardiovascular disease, use aspirin and statin therapy (if not contraindicated) and consider ACE inhibitor therapy to reduce the risk of cardiovascular events. • In patients with prior myocardial infarction, β-blockers should be continued for at least two years after the event. • In patients with symptomatic heart failure, thiazolidinedione treatment should not be used. • In patients with type 2 diabetes with stable congestive heart failure, metformin may be used if estimated glomerular filtration remains >30 mL/min but should be avoided in unstable or hospitalized patients with congestive heart failure. <u>Diabetic 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, in all patients with type 2 diabetes, and in all patients with comorbid hypertension. • Optimize glucose control to reduce the risk or slow the progression of diabetic kidney disease. • Optimize blood pressure control to reduce the risk or slow the progression of diabetic kidney disease. • For people with nondialysis-dependent diabetic kidney disease, dietary protein intake should be approximately 0.8 g/kg body weight per day (the recommended daily allowance). For patients on dialysis, higher levels of dietary protein intake

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	should be considered. • 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) B 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 or changes in potassium when ACE inhibitors, angiotensin receptor blockers, or diuretics are used. • Continued monitoring of urinary albumin–to–creatinine ratio in patients with albuminuria treated with an ACE inhibitor or an angiotensin receptor blocker is reasonable to assess the response to treatment and progression of diabetic kidney disease. • An ACE inhibitor or an angiotensin receptor blocker is not recommended for the primary prevention of diabetic kidney disease 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. • When estimated glomerular filtration rate is <60 mL/min/1.73 m^2, evaluate and manage potential complications of chronic kidney disease. • Patients should be referred for evaluation for renal replacement treatment if they have an estimated glomerular filtration rate <30 mL/min/1.73 m^2. • Promptly refer to a physician experienced in the care of kidney disease 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[3-19]

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		✔								

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
clinically stable patients with left ventricular dysfunction manifested as an ejection fraction ≤40% 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[3-19]

Indication(s)	Combination Products							
	Benazepril and HCTZ	Captropril and HCTZ	Enalapril and HCTZ	Fosinopril and HCTZ	Lisinopril and HCTZ	Moexipril and HCTZ	Quinapril and HCTZ	Trandolapril and Verapamil
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[20]

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
Moexipril and HCTZ	13*/60 to 80	50*/21 to 24	Liver (% not reported)/ Not metabolized	Feces (1) Renal (1)/ Feces (not reported) Renal (60)	1.3/ 5.6 to 14.8
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
Trandolapril and verapamil	10/20 to 35	80/90	Liver, extensive (% not reported)/ Liver, extensive (% not reported)	Feces (66) Renal (33)/ Feces (16) Renal (70)	6/6 to 11

*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[20]

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,	Everolimus, sirolimus	Concurrent use of ACE inhibitors and MTOR inhibitors may result in increased risk of angioedema.

Generic Name(s)	Interaction	Mechanism
perindopril, quinapril, ramipril, trandolapril)		
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 (benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, quinapril, ramipril, trandolapril)	Lithium	Through an unknown mechanism, ACE inhibitors may increase lithium levels, which results in neurotoxicity.
Calcium-channel blocking agents, miscellaneous (verapamil)	Aldosterone blockers	Plasma concentrations and pharmacologic or toxic effects of aldosterone blockers may be increased by verapamil.
Calcium-channel blocking agents, miscellaneous (verapamil)	Carbamazepine	Verapamil appears to impair the hepatic metabolism of carbamazepine. Carbamazepine levels may increase, resulting in an increase in pharmacologic and toxic effects.
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)	Cyclosporine	Verapamil may inhibit cyclosporine metabolism leading to increased cyclosporine levels and toxicity.
Calcium-channel blocking agents, miscellaneous (verapamil)	Digitalis glycosides	Verapamil may alter the pharmacokinetics and increase serum concentrations of digoxin.
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.
Calcium-channel blocking agents, miscellaneous (verapamil)	Everolimus	Pharmacologic effects and plasma concentrations of everolimus may be increased by verapamil.
Calcium-channel blocking agents, miscellaneous (verapamil)	Flecainide	Increased risk of cardiotoxic effects may occur when flecainide and verapamil are coadministered.
Calcium-channel blocking agents, miscellaneous (verapamil)	HMG CoA reductase inhibitors	Verapamil may inhibit the first-pass metabolism of certain HMG CoA reductase inhibitors (e.g., simvastatin and lovastatin) which results in increased plasma concentrations and risk of toxicity.
Calcium-channel blocking agents, miscellaneous (verapamil)	Nondepolarizing muscle relaxants	The effects of the nondepolarizing muscle relaxants may be enhanced and respiratory depression may be prolonged. The mechanism probably involves blockade of calcium-channels in skeletal muscle at the postsynaptic muscle membrane site.
Calcium-channel blocking agents, miscellaneous (verapamil)	Quinidine	Verapamil can prolong the half-life of quinidine by interfering with clearance. There is an increased risk for hypotension, bradycardia, ventricular tachycardia and atrioventricular block.
Calcium-channel blocking agents, miscellaneous	Ranolazine	Plasma concentrations and pharmacologic effects of ranolazine may be increased by co-administration of

Generic Name(s)	Interaction	Mechanism
(verapamil)		verapamil.
Calcium-channel blocking agents, miscellaneous (verapamil)	Rifampin	First-pass hepatic metabolism of verapamil may be increased, resulting in lowered bioavailability and reduced effectiveness of oral verapamil.
Calcium-channel blocking agents, miscellaneous (verapamil)	β-Blockers	Verapamil may inhibit oxidative metabolism of certain β-blockers. The effects of both drugs may be increased.
Calcium-channel blocking agents, miscellaneous (verapamil)	Colchicine	Plasma concentrations of colchicine may be increased by verapamil. Colchicine toxicity may occur.
Calcium-channel blocking agents, miscellaneous (verapamil)	Dofetilide	Verapamil can increase portal blood flow, increasing the rate of dofetilide absorption. There may be an increased risk of ventricular arrhythmias, including torsades de pointes.
Calcium-channel blocking agents, miscellaneous (verapamil)	Macrolides and ketolides	Macrolides and ketolides may increase the plasma concentrations and pharmacological effects of verapamil.
Calcium-channel blocking agents, miscellaneous (verapamil)	Narcotic analgesics	Verapamil may increase plasma concentrations of narcotic analgesics when used concurrently.
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[3-20]

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[3-20]

Adverse Event	Benaze-pril and HCTZ	Capto-pril and HCTZ	Enala-pril and HCTZ	Fosino-pril and HCTZ	Lisino-pril and HCTZ	Moexi-pril and HCTZ	Quina-pril and HCTZ	Trandola-pril and Verapamil
Cardiovascular								
Angina	-	0.2 to 0.3	-	-	-	-	-	✔
Angioedema	-	-	-	-	-	-	-	0.15
Atrioventricular block first degree	-	-	-	-	-	-	-	3.9
Atrioventricular block second degree	-	-	-	-	-	-	-	✔
Bradycardia	-	-	-	-	-	-	-	1.8
Bundle branch block	-	-	-	-	-	-	-	✔
Cardiac arrest	-	✔	-	-	-	-	-	
Cerebrovascular accident	-	✔	-	-	-	-	-	
Chest pain	-	1	-	0.5 to <2.0	-	>1	1	2.2
Hypotension	0.6	✔	-	-	1.4	>1	-	✔
Myocardial infarction	-	0.2 to 0.3	-	-	-	-	-	✔
Near syncope	-	-	-	-	-	-	-	✔
Nonspecific ST-T changes	-	-	-	-	-	-	-	✔
Orthostatic hypotension	0.3 to 3.5	✔	2.3	1.8	0.5	<1	≥0.5 to <1.0	
Palpitations	-	1	0.5 to 2.0	-	-	-	≥0.5 to <1.0	✔
Premature ventricular contractions	-	-	-	-	-	-	-	✔
Tachycardia	-	1	-	-	-	-	-	✔
Central Nervous System								
Depression	-	✔	-	-	-	-	-	
Dizziness	6.3	-	8.6	3.2	7.5	1.4	4.8	3.1
Drowsiness	-	-	-	-	-	-	-	✔
Fatigue	5.2	-	3.9	3.9	3.7	1	2.9	2.8
Headache	3.1	-	5.5	7	5.2	>1	6.7	8.9
Hypesthesia	-	-	-	-	-	-	-	✔
Insomnia	✔	-	0.5 to 2.0	-	-	-	1.2	
Loss of balance	-	-	-	-	-	-	-	✔
Paresthesia	-	-	-	-	-	-	-	✔
Somnolence/drowsiness	1.2	✔	-	-	-	-	1.2	
Vertigo	-	-	-	-	-	-	-	✔
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	>1	-	✔
Stevens-Johnson syndrome	✔	✔	✔	✔	-	-	✔	
Gastrointestinal								
Abdominal pain	-	-	-	-	-	-	1.7	
Constipation	-	-	-	-	-	-	-	3.3
Diarrhea	0.3 to 1.0	✔	2.1	0.5 to <2.0	2.5	>1	1.4	1.5
Dry mouth	-	-	-	-	-	-	-	✔
Dysgeusia	-	2 to 4	-	-	-	-	-	
Dyspepsia	-	✔	-	-	-	-	-	✔
Hepatitis	-	✔	-	-	-	-	-	
Jaundice	✔	✔	✔	✔	-	<1	✔	

Adverse Event	Benaze-pril and HCTZ	Capto-pril and HCTZ	Enala-pril and HCTZ	Fosino-pril and HCTZ	Lisino-pril and HCTZ	Moexi-pril and HCTZ	Quina-pril and HCTZ	Trandola-pril and Verapamil
Nausea	1.4	-	2.5	✔	2.2	>1	✔	1.5
Pancreatitis	-	✔	-	-	-	-	-	
Genitourinary								
Decreased libido	-	✔	-	✔	-	-	-	
Endometriosis	-	-	-	-	-	-	-	✔
Hematuria	-	-	-	-	-	-	-	✔
Impotence	1.2		2.2	-	1.2	>1	≥0.5 to <1.0	✔
Nocturia	-	-	-	-	-	-	-	✔
Oliguria	-	0.1 to 0.2	-	-	-	-	-	
Polyuria	-	-	-	-	-	-	-	✔
Proteinuria	-	-	-	-	-	-	-	✔
Musculoskeletal								
Arthralgias	-	-	-	-	-	-	-	✔
Back pain	-	-	-	-	-	-	-	2.2
Gout	-	-	-	-	-	-	-	✔
Hypertonia	1.5	-	-	-	-	-	-	
Joint pain	-	-	-	-	-	-	-	1.7
Muscle cramps	-	-	2.7	-	2	-	-	
Musculoskeletal pain	-	-	-	2	-	-	-	
Myalgia	-	✔	-	-	-	-	2.4	✔
Pain in the extremity	-	-	-	-	-	-	-	1.1
Respiratory								
Bronchitis	-	-	-	-	-	-	1.2	1.5
Cough	2.1	0.5 to 2.0	3.5	5.6	3.9	3	3.2	4.6
Dyspnea	-	-	-	-	-	-	-	1.3
Rhinitis	-	✔	-	-	-	-	2	
Upper respiratory tract congestion	-	-	-	-	-	-	-	2.4
Upper respiratory tract infection	-	-	-	2.3	2.2	>1	1.3	5.4
Miscellaneous								
Abnormal mentation	-	-	-	-	-	-	-	✔
Anemia	-	≤0.2	-	-	-	-	-	
Angioedema	0.3	0.1	0.5 to 2.0	0.5 to <2.0	0.3 to 1.0	>1	0.1	
Anxiety	-	-	-	-	-	-	-	✔
Asthenia	-	✔	2.4	-	1.8	<1	≥0.5 to <1.0	
Blurred vision	-	✔	-	-	-	-	-	
Decreased leukocytes	-	-	-	-	-	-	-	✔
Decreased neutrophils	-	-	-	-	-	-	-	✔
Edema	-	-	-	-	-	-	-	1.3
Eosinophilia	-	✔	-	-	-	-	-	
Epistaxis	-	-	-	-	-	-	-	✔
Fever	-	✔	-	-	-	-	-	
Increased liver enzymes	-	-	-	-	-	-	-	2.8
Malaise	-	-	-	-	-	-	-	✔
Neutropenia	-	✔	-	0.5 to <2.0	-	-	-	
Syncope	-	✔	-	-	-	<1	-	0.1

Adverse Event	Benaze-pril and HCTZ	Capto-pril and HCTZ	Enala-pril and HCTZ	Fosino-pril and HCTZ	Lisino-pril and HCTZ	Moexi-pril and HCTZ	Quina-pril and HCTZ	Trandola-pril and Verapamil
Viral infection	-	-	-	-	-	-	1.9	
Weakness	-	-	-	-	-	-	-	✔

HCTZ=hydrochlorothiazide
✔ Percent not specified
- Event not reported

Table 9. Boxed Warning for the Angiotensin-Converting Enzyme Inhibitors[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 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[3-20]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Benazepril	Hypertension: Tablet: initial, 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
Moexipril and HCTZ	Hypertension: Tablet: initial, 7.5-12.5, 15-12.5, or 15-25 mg/day; maintenance, titrate dose by clinical effect; maximum, 30-50 mg/day	Safety and efficacy in children have not been established.	Tablet: 7.5-12.5 mg 15-12.5 mg 15-25 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
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
Trandolapril and verapamil	Hypertension: Extended-release tablet: 1 to 4-120 to 180 mg/day in a single or divided dose(s)	Safety and efficacy in children have not been established.	Extended-release tablet: 1-240 mg 2-180 mg 2-240 mg 4-240 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.[40] (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.[41] (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.[42] (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.[43] (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.[44] (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.[45] (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.[46] (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.[47] (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[48] (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.[49] (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.[50] (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.[51] (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.[52] (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.[53] (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[54] (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[55] (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[56] (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[57] (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.[58] (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.[59] (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[60]	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.[61] (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.[62] (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.[63] (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.[64] (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.[65] (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.[66] (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[67] (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[68] (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.[69] (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.[70] (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.[71] (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.[72] (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.[73] (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.[74] (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[75] (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[76] (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[77] (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.[78] (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.[79] (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.[80] (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.[81] (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.[82] (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.[83] (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[84] (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).
Kober et al.[85] (1995) TRACE Trandolapril 1 to 4 mg QD vs	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	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,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo Medication was started between day 3 and 7 after the myocardial infarction.			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	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.
Galløe et al.[86] (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).

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).
Galloe et al.[87] (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). 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).
Lee et al.[88] (2004) ARBs vs placebo (±ACE inhibitor)	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ACE inhibitor monotherapy				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). Secondary: Not reported
Neutel et al.[90] (2005) SELECT Benazepril and amlodipine 20-5	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
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 mg/day for 8 weeks	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). Secondary: Not reported
Fogari et al.[92] (1997) Benazepril 10 mg QD	DB, MC, PC, RCT Men and women 24 to 73 years of age (mean 55 years) with	N=448 8 weeks	Primary: Reduction in mean sitting DBP Secondary:	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs amlodipine and benazepril 2.5-10 to 5-10 mg QD (fixed-dose combination product)	HTN inadequately controlled with ACE inhibitor monotherapy		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)	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 titrated to 10-40 mg/day after 4 weeks (fixed-dose combination product) (Group 2) Study 2:	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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)				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 product) vs nifedipine 30 to 60 mg/day <u>Study 2:</u>	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Amlodipine and benazepril 5-10 mg to 5-20 mg QD (fixed-dose combination product) vs amlodipine 5 to 10 mg QD				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, 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 (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]	DB, MC, RCT	N=10,704	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(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	Patients >60 years of age with HTN and at high risk of cardiovascular events	Analysis performed at 6 months (complete trial duration 5 years)	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	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 amlodipine 10 mg/day for 4 weeks vs olmesartan 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, 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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				
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) Captopril and HCTZ 50-25 mg/day (fixed-dose combination) vs	DB, MC, RCT Patients with mild-to-moderate arterial HTN (sitting DBP >95 mm Hg and/or SBP >160 mm Hg) inadequately controlled by	N=397 12 weeks	Primary: Reduction in sitting DBP and SBP Secondary: Percentage of patients responding to therapy	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
amlodipine and benazepril 5-10 mg/day (fixed-dose combination)	monotherapy with an ACE inhibitor, calcium-channel blocking agent or diuretic		(DBP<90 mm Hg, reduction in DBP ≥10 mm Hg or SBP ≥20 mm Hg, or SBP <150 mm Hg)	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 20 mg vs bisoprolol and HCTZ 2.5-6.25, 5-6.25, or 10-6.25	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
mg/day (fixed-dose combination product) 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.
Ruilope et al.[102] (2001) Enalapril 5 mg QD (titration to 10 mg followed by 20 mg was allowed every 3 weeks) vs	DB, MC, PG, RCT Patients greater than 65 years of age with essential HTN, either newly diagnosed or for whom a change in existing antihypertensive medication is	N=334 12 weeks	Primary: Mean change from baseline in sitting SBP Secondary: Normalization rate for sitting SBP and DBP, response rate for sitting SBP and DBP, mean change	Primary: No significant difference between groups in change from baseline in sitting SBP was observed (P=0.76). 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
eprosartan 600 mg QD (titration to 800 mg QD was allowed after 3 weeks)	indicated due to poor control		from baseline in DBP	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 vs nisoldipine 10 to 60 mg/day	DB, PRO, RCT Patients between the ages of 40 and 74 years with NIDDM, baseline DBP ≥90 mm Hg and receiving no antihypertensive medications at the time of randomization	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 the incidence and progression of complications of diabetes; compare enalapril 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. 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			nisoldipine as a first-line antihypertensive agent Secondary: Incidence of MI	
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.
Tatti et al.[106] (1998) FACET Fosinopril 20 mg QD	OL, PRO, RCT Men and women, diagnosed with HTN (SBP >140 mm Hg or DBP >90 mm Hg) and non-insulin	N=380 Up to 3.5 years	Primary: Blood pressure Secondary: Fasting serum glucose, serum creatinine, plasma	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs amlodipine 10 mg QD If blood pressure was not controlled on monotherapy, the other study drug was added.	dependent diabetes		insulin, HbA_{1c}, TC, HDL-C, TG, fibrinogen, microalbuminuria	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 patients responded to treatment (defined by a decrease in office DBP to <90 mm Hg or ≥10 mm Hg decrease from	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 treatment group. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
baseline).				
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 month before active treatment, and had a sitting DBP of >95 and <114 mm Hg	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. 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]	DB, DD, RCT, XO	N=47	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2008) Lisinopril 5mg QD vs atenolol 25 mg QD vs lisinopril 5 mg and atenolol 25 mg QD vs placebo	Patients ≥ 40 years enrolled in a HTN or anticoagulation clinic	16 weeks	Reduction in blood pressure Secondary: Not reported	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 vs felodipine 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 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

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.				
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 vs amlodipine 5 to 10 mg QD and valsartan 160 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	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:

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			baseline)	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) at week 12 and week 36, percentage of patients who required add-on therapy	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). 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 achieving adequate blood pressure control. The study did not specifically analyze the effects	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 achieving blood pressure control (<140/90 mm Hg), proportion achieving SBP control (<140 mm	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 (-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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
of HCTZ on either treatment regimen.			Hg), safety	(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 vs azilsartan (AZL) 20mg titrated to 80 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ramipril (RAM) 2.5 mg titrated to 10 mg				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 pressure, 24-hour blood pressure load, treatment response, blood pressure control	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).
O'Brien et al.[119] (2007)	3 OL studies	N=67	Primary: Change in daytime	Primary: Aliskiren coadministered with HCTZ (P=0.0007) or ramipril (P=0.03) led

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 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 weeks	Men and women 18 to 80 years with ambulatory SBP ≥140 and ≤180 mm Hg without treatment	6 to 9 weeks	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	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.
Tytus et al.[120] (2007) Trandolapril 1 to 4 mg/day	MC, OL, PRO Patients with stage 1 or 2 HTN who were treatment naïve (82%) or	N=1,683 26 weeks	Primary: Percentage of patients reaching target blood pressure at 14 weeks	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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.	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		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	<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
Pauly et al.[122] (1994) Trandolapril 4 mg QD vs	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:	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
captopril 50 mg BID If blood pressure was not normalized at 8 weeks, HCTZ 25 mg was added.			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)	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
Karlberg et al.[124] (2000) Trandolapril 2 mg/day vs	DB, MC, PRO, RCT, XO Patients with uncomplicated primary HTN (sitting DBP	N=226 2 months	Primary: Change in blood pressure and rate pressure product Secondary:	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
verapamil 240 mg/day vs trandolapril and verapamil 2-180 mg/day (fixed-dose combination)	between 95 and 115 mm Hg) between the ages of 20 to 80 years		Predictive value of plasma concentrations of active renin regarding the blood pressure response to the different treatment regimens, safety	(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 needed (step 2), then increase doses of both (step 3), then add trandolapril (step 4) (non-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)				
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 captopril and HCTZ 50-25 mg QD (fixed-dose combination) (CH) After 16 weeks,	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 parameters	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). 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
patients were switched to the other fixed combination for an additional 16 weeks.				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]). 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:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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
Van Bortel et al.[130] (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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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
Baguet et al.[131] (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.	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
Although cicletanine*, furosemide and spironolactone were considered for inclusion, none of the trials relating to these agents satisfied all inclusion criteria.				Secondary: Not reported
Diabetes/Diabetic Nephropathy/Renal Dysfunction				
Bakris et al.[132] (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	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(fixed-dose combination product)				
Hou et al.[133] (2007) ROAD 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.	OL, PRO, RCT Patients aged 18 to 70 years with proteinuria and chronic renal insufficiency who did not have diabetes	N=360 3.7 years (median follow-up)	Primary: Time to composite of doubling of serum creatinine, ESRD or death Secondary: Changes in level of proteinuria, rate of progression of renal disease	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). 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.[134] (2008) GUARD	DB, RCT Hypertensive, albuminuric type 2	N=322 52 weeks	Primary: Change in urinary albumin to creatinine ratio	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Benazepril and HCTZ (fixed-dose combination) vs amlodipine and benazepril (fixed-dose combination)	diabetic patients, mean age 58 years were randomized to receive either initial fixed-dose combination product		after 1 year of initial treatment with either fixed-dose combination, blood pressure reductions Secondary: Proportion who progressed to overt diabetic nephropathy, safety	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%).
Esnault et al.[135] (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.[136] (2004)	DB, MC, PG, RCT	N=250	Primary: Change in the GFR	Primary: After five years, GFR decreased by 17.9 mL/minute/1.73 m^2 with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
DETAIL Enalapril 20 mg/day vs telmisartan 80 mg/day	Patients aged 35 to 80 years with type 2 diabetes and HTN	5 years	Secondary: Annual changes in GFR, serum creatinine level, urinary albumin excretion, and blood pressure; rates of ESRD and cardiovascular events; all-cause mortality	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.
Mogensen et al.[137] (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	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
monotherapy or combination therapy.				
Fried et al.[138] (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 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	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. 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[139] (2006) DREAM Ramipril up to 15	DB, MC, PC, PRO, RCT, 2-by-2 factorial design Adults aged 30 years or more with	N=5,269 3 years (median)	Primary: Composite of newly diagnosed diabetes or death Secondary:	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:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day vs placebo	impaired fasting glucose and/or impaired glucose tolerance and no previous cardiovascular disease		Regression to normoglycemia, glucose levels, composite of cardiac and renal events (were not yet analyzed at the time of this publication)	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 (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[140] (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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Uresin et al.[141] (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 changes in biomarkers (plasma renin concentration, plasma renin activity, aldosterone)	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%). 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.[142]	DB, MC, RCT	N=1,094	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2001) AASK Ramipril 2.5 to 10 mg QD vs amlodipine 5 to 10 mg QD	African American patients, age 18 to 70 years old, with hypertensive renal disease (GFR 20 to 65 mL/min)	4 years	Rate of change in GFR (GFR slope) Secondary: Composite of: confirmed reduction GFR by 50% or by 25 mL/min for baseline, ESRD	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.[143] (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.[144] (2010) Ramipril 10 mg and atorvastatin 10 mg QD (conventional therapy)	RCT, OL Patients with a clinical diagnosis of idiopathic chronic glomerulonephritis and urine protein-creatinine	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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	ratio >1 g/g			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.
Chrysostomou et al.[145] (2006) Ramipril 5 mg/day plus spironolactone 25 mg/day and placebo vs ramipril 5 mg/day plus irbesartan 150 mg/day 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ramipril 5 mg/day plus placebo and placebo vs spironolactone 25 mg/day plus irbesartan 150 mg/day and ramipril 5 mg/day				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.
Nakao et al.[146] (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.[147] (2004) BENEDICT Trandolapril 2	DB, MC, RCT Patients ≥40 years with type 2 diabetes (not exceeding 25 years) and HTN	N=1,204 3.6 years (median)	Primary: Development of persistent microalbuminuria comparing combination	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day vs verapamil SR 240 mg/day vs trandolapril and verapamil SR 2-180 mg/day (fixed-dose combination) vs placebo	(SBP ≥130 mm Hg and/or DBP ≥85 mm Hg) but with normoalbuminuria (urinary albumin excretion rate of <20 mcg/minute)		therapy to placebo, acceleration factor Secondary: Primary end point comparing trandolapril and verapamil monotherapy to placebo, blood pressure, adverse events	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.
Casas et al.[148] (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,	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
calcium-channel blocking agents, or combinations) Specific agents and doses were not specified.				Compared to other drugs, ACE inhibitors or ARBs had no effect on the GFR.
Strippoli et al.[149] (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.[150] (2006)	MA Patients with	N=12,067 (49 trials)	Primary: All-cause mortality, ESRD,	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ACE inhibitors vs placebo or ARBs vs placebo or ACE inhibitors vs ARBs	diabetic kidney disease	≥6 months	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	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). 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Miscellaneous				
Montalescot et al.[151] (2009) 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	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 Secondary: Changes in other inflammatory markers such as troponin I	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: 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.[152] (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	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			the primary analysis	
Belluzzi et al.[153] (2009) Ramipril 5mg QD vs placebo	DB, PC, RCT Adults with lone atrial fibrillation without heart disease or HTN	N=62 3 years	Primary: Relapse of atrial fibrillation as determined by clinical assessment, ECG, 24 hour Holter monitor, and questionnaire collection. Secondary: Not reported	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). Secondary: Not reported
Hansson et al.[154] (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).[155] 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).[156] 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).[157]

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).[158]

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®*	$$	$
Captopril	tablet	N/A	N/A	$$$$
Enalapril	solution, tablet	Epaned®, Vasotec®*	$$$$$	$$$$
Fosinopril	tablet	N/A	N/A	$
Lisinopril	solution, tablet	Prinivil®*, Qbrelis®, Zestril®*	$$$$$	$
Moexipril	tablet	N/A	N/A	$$$$
Perindopril	tablet	Aceon®*	N/A	$$
Quinapril	tablet	Accupril®*	$$$	$
Ramipril	capsule	Altace®*	$$$$	$
Trandolapril	tablet	N/A	$$	$
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®*	$$	$
Moexipril and HCTZ	tablet	N/A	N/A	$$$
Quinapril and HCTZ	tablet	Accuretic®*	$$$	$$$
Trandolapril and verapamil	extended-release tablet	Tarka®	$$$$	$$$$

*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.[3-20] The ACE inhibitors are available as single entity products, as well as in combination with hydrochlorothiazide or verapamil. 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.[21-39] Thiazide-type diuretics are frequently recommended as initial therapy in patients with uncomplicated hypertension.[32-37] 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).[32] Several guidelines consistently recommend that the selection of an antihypertensive agent be based on compelling indications for use.[32-39] Most patients will require more than one antihypertensive medication to achieve blood pressure goals.[32-38]

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.[40-149] 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.[32-37,155-157] 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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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.[21,22] 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.[21,22] Valsartan is also available in combination with nebivolol, a β-blocker without intrinsic sympathomimetic activity.

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 and valsartan-nebivolol. This class was last reviewed in August 2015.

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®*	none
Eprosartan	tablet	N/A	eprosartan
Irbesartan	tablet	Avapro®*	irbesartan
Losartan	tablet	Cozaar®*	losartan
Olmesartan	tablet	Benicar®*	none
Telmisartan	tablet	Micardis®*	none
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

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Olmesartan and amlodipine and hydrochlorothiazide	tablet	Tribenzor®*	none
Olmesartan and hydrochlorothiazide	tablet	Benicar HCT®*	none
Telmisartan and amlodipine	tablet	Twynsta®*	none
Telmisartan and hydrochlorothiazide	tablet	Micardis HCT®*	none
Valsartan and hydrochlorothiazide	tablet	Diovan HCT®*	valsartan and hydrochlorothiazide
Valsartan and nebivolol	tablet	Byvalson®	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 angiotensin II receptor antagonists are summarized in Table 2.

Table 2. Treatment Guidelines Using the Angiotensin II Receptor Antagonists

Clinical Guideline	Recommendations
American College of Cardiology/American Heart Association: **2007 Chronic Angina Focused Update of the 2002 Guidelines for the Management of Patients With Chronic Stable Angina (2007)**[23]	• Aspirin should be started at 75 to 162 mg/day and continued indefinitely in all patients, unless contraindicated. • Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with an increased risk of bleeding and should be monitored closely. • Patients with hypertension and established coronary artery disease (CAD) should be treated with blood pressure medication(s) as tolerated, including angiotensin-converting enzyme inhibitors (ACE inhibitors) and/or β-adrenergic antagonists (β-blockers) with the addition of other medications as needed to achieve blood pressure goals of <140/90 or <130/80 mm Hg for patients with chronic kidney disease or diabetes. • Long-acting calcium-channel blocking agents or long-acting nitrates may be used if β-blockers are contraindicated. Immediate-release and short-acting dihydropyridine calcium channel blockers can increase adverse cardiac events and should not be used. • Long-acting calcium channel blockers or long-acting nitrates may be used with β-blockers if initial treatment is not successful. • ACE inhibitors should be used indefinitely in patients with a left ventricular ejection fraction (LVEF) of ≤40% and in those with hypertension, diabetes or chronic kidney disease, unless contraindicated. • ACE inhibitors should also be used indefinitely in patients at lower risk (mildly reduced or normal LVEF in whom cardiovascular risk factors remain well controlled and revascularization has been performed), unless contraindicated. • Angiotensin II receptor blockers (ARBs) are recommended in patients with hypertension, those who have an indication for an ACE inhibitor and are intolerant to them, who have heart failure, or who have had a myocardial infarction (MI) and have a LVEF of ≤40%. • ARBs may be considered in combination with an ACE inhibitor for heart failure due to left ventricular systolic dysfunction. • Aldosterone blockade is recommended in patients post-MI without significant renal dysfunction or hyperkalemia who are already receiving therapeutic doses of an ACE inhibitor and a β-blocker, have a LVEF ≤40% and have either diabetes or heart failure. • It is beneficial to start and continue β-blocker therapy indefinitely in all patients who have had a MI, acute coronary syndrome or left ventricular dysfunction with or without heart failure symptoms, unless contraindicated.

Clinical Guideline	Recommendations
	• Annual influenza vaccination is recommended in patients with cardiovascular disease.
European Society of Cardiology: **Guidelines on the Management of Stable Coronary Artery Disease (2013)**[24]	<u>General management of stable coronary artery disease (SCAD) patients</u> • The goal of management of SCAD is to reduce symptoms and improve prognosis. • The management of CAD patients encompasses lifestyle modification, control of CAD risk factors, evidence-based pharmacological therapy, and patient education. <u>General considerations for pharmacological treatments in SCAD patients</u> • 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. <u>Pharmacological treatments for angina/ischemia relief in SCAD patients</u> • Short-acting nitrates are recommended. • First-line treatment is indicated with ß-blockers and/or calcium channel blockers to control heart rate and symptoms. • For second-line treatment it is recommended to add long-acting nitrates or ivabradine or nicorandil* or ranolazine, according to heart rate, blood pressure, and tolerance. • For second-line treatment, trimetazidine* may be considered. • 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 β-blockers avoided. <u>Pharmacological treatments for event prevention in SCAD patients</u> • Low-dose aspirin daily is recommended in all SCAD patients. • Clopidogrel is indicated as an alternative in case of aspirin intolerance. • Statins are recommended in all SCAD 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. • β-blockers are recommended as a first line treatment. • Calcium antagonists are recommended if β-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 (aminophylline, bamiphylline*) or non-pharmacological treatments such as neurostimulatory techniques may be considered in patients with symptoms refractory to the above listed drugs.
American College of Physicians/ American College of Cardiology Foundation/ American Heart Association/ American Association	<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.

Clinical Guideline	Recommendations
for Thoracic Surgery/ Preventive Cardiovascular Nurses Association/ Society of Thoracic Surgeons: **Management of Stable Ischemic Heart Disease (2012)**[25]	• 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 Management of Patients With Non–ST-Elevation Acute Coronary Syndromes (2014)**[26]	<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
	  ○ 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,

Clinical Guideline	Recommendations
	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 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

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	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. ○ 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

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	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 patients treated with ticagrelor and 81 to 325 mg daily in all other patients. ○ 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. ○ 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 ○ 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. ○ 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: **Guideline for the**	<u>Pharmacological treatment of ischemia</u> • Early initiation of β-blocker treatment is recommended in patients with ongoing ischemic symptoms and without contraindications.

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Management of Acute Coronary Syndromes in Patients Presenting Without Persistent ST-Segment Elevation (2015)[27]	• 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.
	  ○ 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.
	• 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.

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	• 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. 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 CHADS2-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. • 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 CHADS2-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.
American College of Cardiology/American Heart Association: **Guideline for the Management of ST-Elevation Myocardial Infarction (2013)**[28]	Routine medical therapies: β-blockers • 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. Routine medical therapies: renin-angiotensin-aldosterone system inhibitors • An ACE inhibitor should be administered within the first 24 hours to all patients

Clinical Guideline	Recommendations
	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 (2012)**[29]	<u>Routine therapies in the acute, subacute and long term phase of STEMI</u> • Active smokers with STEMI must receive counseling and be referred to a smoking cessation program. • Each hospital participating in the care of STEMI patients must have a smoking cessation protocol. • Exercise-based rehabilitation is recommended. • Antiplatelet therapy with low dose aspirin (75 to 100 mg) is indicated indefinitely after STEMI. • In patients intolerant to aspirin, clopidogrel is indicated as an alternative. • Dual antiplatelet therapy with a combination of aspirin and prasugrel or aspirin and ticagrelor is recommended (over aspirin and clopidogrel) in patients treated with PCI. • Dual antiplatelet therapy with aspirin and an oral ADP receptor antagonist must be continued for up to 12 months after STEMI, with a strict minimum of 1 month for patients receiving bare metal stent and 6 months for patients receiving drug-eluting stent. • In patients with left ventricular thrombus, anticoagulation should be instituted for a minimum of 3 months. • In patients with a clear indication for oral anticoagulation (e.g. atrial fibrillation with CHA2DS2-VASc Score ≥2 or mechanical valve prosthesis), oral anticoagulation must be implemented in addition to antiplatelet therapy. • If patients require triple antithrombotic therapy, combining dual antiplatelet therapy and oral anticoagulant, e.g. because of stent placement and an obligatory indication for oral anticoagulation, the duration of dual antiplatelet therapy should be minimized to reduce bleeding risk. • 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 1 year in patients with STEMI who did not receive a stent. • Gastric protection with a proton pump inhibitor should be considered for the duration of DAPT therapy in patients at high risk of bleeding. • 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. • Intravenous β-blockers must be avoided in patients with hypotension or heart failure. • Intravenous β-blockers should be considered at the time of presentation in patients without contraindications, with high blood pressure, tachycardia, and no signs of heart failure.

Clinical Guideline	Recommendations
	• 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. • Reassessment of LDL-cholesterol should be considered after 4–6 weeks to ensure that a target value of ≤70 mg/dL has been reached. • Verapamil may be considered for secondary prevention in patients with absolute contraindications to β-blockers and no heart failure. • 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.

National Institute for Health and Clinical Excellence: **Myocardial Infarction: cardiac rehabilitation and prevention of further cardiovascular disease (2013)**[30]	Drug therapy
	• Offer all people who have had an acute MI treatment with the following drugs:
	  ○ ACE inhibitor
	  ○ Dual antiplatelet therapy (aspirin plus a second antiplatelet agent)
	  ○ β-blocker
	  ○ Statin
	
	Antiplatelet therapy
	• Offer aspirin to all people after an MI and continue indefinitely, unless they are aspirin intolerant or have an indication for anticoagulation.
	• Offer aspirin to people who have had an MI more than 12 months ago and continue it indefinitely.
	• For patients with aspirin hypersensitivity, clopidogrel monotherapy should be considered as an alternative treatment.
	• Special considerations should be made for people with dyspepsia.
	• After appropriate treatment, people with a history of aspirin-induced ulcer bleeding whose ulcers have healed and who are negative for Helicobacter pylori should be considered for treatment in line with dyspepsia.
	• Ticagrelor in combination with low-dose aspirin is recommended for up to 12 months as a treatment option in adults with ACS (STEMI, PCI, or NSTEMI).
	• Offer clopidogrel as a treatment option for up to 12 months to people who have had an NSTEMI, regardless of treatment, or people who have had a STEMI and received a bare-metal or drug-eluting stent.
	• Offer clopidogrel as a treatment option for at least one month and consider continuing for up to 12 months in people who have had a STEMI and medical management with or without reperfusion treatment with a fibrinolytic agent.
	• Continue the second antiplatelet agent for up to 12 months in people who have had a STEMI and who received CABG surgery.
	• Offer clopidogrel instead of aspirin to people who also have other clinical vascular disease (had an MI and stopped dual antiplatelet therapy or had an MI more than 12 months ago).
	
	Antiplatelet therapy in people with an indication for anticoagulation
	• Take bleeding risk, thromboembolic risk, and cardiovascular risk into account when deciding which people who have had an MI and have an indication for

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	anticoagulation. • Unless there is a high risk of bleeding, continue anticoagulation and add aspirin to treatment in people who have had an MI who otherwise need anticoagulation and who have had their condition managed medically or have undergone balloon angioplasty or have undergone CABG surgery. • Continue anticoagulation and add clopidogrel to treatment in people who have had an MI, who have undergone PCI with bare-metal or drug-eluting stents and who otherwise need anticoagulation. • Offer clopidogrel with warfarin to people with a sensitivity to aspirin who otherwise need anticoagulation and aspirin and who have had an MI. • Do not routinely offer warfarin in combination with prasugrel or ticagrelor to people who need anticoagulation who have had an MI. • After 12 months since the MI, continue anticoagulation and take into consideration the need for ongoing antiplatelet therapy, taking into account all of the following: indication for anticoagulation, thromboembolic risk, bleeding risk, cardiovascular risk and the person's wishes. • Do not add a new oral anticoagulant (rivaroxaban, apixaban or dabigatran) in combination with dual antiplatelet therapy in people who otherwise need anticoagulation, who have had an MI. • Consider using warfarin and discontinuing treatment with a new oral anticoagulant (rivaroxaban, apixaban, or dabigatran) in people who otherwise need anticoagulation and who have had an MI, unless there is a specific clinical indication to continue it.
American College of Cardiology/American Heart Association: **Guideline for the Management of Heart Failure (2013)**[31]	Treatment of Stage A heart failure (HF) • Hypertension and lipid disorders should be controlled in accordance with guidelines to lower the risk of HF. (Level of Evidence (LoE): A) • Other conditions that may lead to or contribute to HF, such as obesity, diabetes mellitus, tobacco use, and known cardiotoxic agents, should be controlled or avoided. (LoE: C) Treatment of Stage B heart failure • In patients with a history of MI and reduced EF, ACE inhibitors or ARBs should be used to prevent HF. (LoE: A) • In patients with MI and reduced EF, evidence-based β-blockers (using one of three proven to reduce mortality [i.e., bisoprolol, carvedilol, and sustained-release metoprolol succinate]) should be used to prevent HF. (LoE: B) • In patients with MI, statins should be used to prevent HF. (LoE: A) • ACE inhibitors and β-blockers should be used in all patients with a reduced EF to prevent symptomatic HF, even if they do not have a history of MI. (LoE: A and C, respectively) • Blood pressure should be controlled to prevent symptomatic HF. (LoE: A) • Nondihydropyridine calcium channel blockers may be harmful in patients with low LVEF. (LoE: C) Pharmacological treatment for Stage C HFrEF • Recommendations for patients in Stages A and B are recommended where appropriate for patients in Stage C. (LoE: A, B, and C as appropriate) • Diuretics are recommended in patients with HFrEF who have evidence of fluid retention, unless contraindicated, to improve symptoms. (LoE: C) • ACE inhibitors are recommended in patients with HFrEF and current or prior symptoms, unless contraindicated, to reduce morbidity and mortality. ARBs are recommended as alternative therapy in ACE inhibitor intolerant patients. (LoE: A) • Use of one of the three β-blockers proven to reduce mortality is recommended for all patients with current or prior symptoms of HFrEF, unless contraindicated, to

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	reduce morbidity and mortality. (LoE: A) • Aldosterone receptor antagonists are recommended in patients with NYHA class II–IV HF and who have LVEF of ≤35%, unless contraindicated, to reduce morbidity and mortality. Patients with NYHA class II HF should have a history of prior cardiovascular hospitalization or elevated plasma natriuretic peptide levels to be considered for aldosterone receptor antagonists. Creatinine should be ≤2.5 mg/dL in men or ≤2.0 mg/dL in women (or estimated glomerular filtration rate >30 mL/min/1.73 m^2), and potassium should be <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) • The combination of hydralazine and isosorbide dinitrate is recommended to reduce morbidity and mortality for patients self-described as African Americans with NYHA class III–IV HFrEF receiving optimal therapy with ACE inhibitors and β-blockers, unless contraindicated. (LoE: A) • Digoxin can be beneficial in patients with HFrEF, unless contraindicated, to decrease hospitalizations for HF. (LoE: B) • Patients with chronic HF with permanent/persistent/paroxysmal AF and an additional risk factor for cardioembolic stroke (history of hypertension, diabetes mellitus, previous stroke or transient ischemic attack, or ≥75 years of age) should receive chronic anticoagulant therapy. (LoE: A) • Statins are not beneficial as adjunctive therapy when prescribed solely for the diagnosis of HF in the absence of other indications for their use. (LoE: A) • Calcium channel blockers are not recommended as routine treatment for patients with HFrEF. (LoE: A) <u>Pharmacological treatment for Stage C HFpEF</u> • Blood pressure should be controlled according to published clinical practice guidelines. (LoE: B) • Diuretics should be used for relief of symptoms due to volume overload. (LoE: C) • The use of β-blocking agents, ACE inhibitors, and ARBs in patients with hypertension is reasonable to control blood pressure in patients with HFpEF. (LoE: C) <u>Treatment of Stage D (advanced/refractory) HF</u> • Fluid restriction (1.5 to 2 L/d) is reasonable, especially in patients with hyponatremia, to reduce congestive symptoms. (LoE: C) • Until definitive therapy (e.g., coronary revascularization, mechanical circulatory support, heart transplantation) or resolution of the acute precipitating problem, patients with cardiogenic shock should receive temporary intravenous inotropic support to maintain systemic perfusion and preserve end-organ performance. (LoE: C) • Continuous intravenous inotropic support is reasonable as "bridge therapy" in patients with stage D HF refractory to medical therapy and device therapy who are eligible for and awaiting mechanical circulatory support or cardiac transplantation. (LoE: B) • Long-term use of either continuous or intermittent, intravenous parenteral positive inotropic agents, in the absence of specific indications or for reasons other than palliative care, is potentially harmful in the patient with HF. (LoE: B)
Heart Failure Society of America: **Heart Failure Society of America 2010 Comprehensive**	<u>Patients with left ventricular systolic dysfunction</u> • ACE inhibitors should be used in all patients with a LVEF ≤40%, unless otherwise contraindicated. • ARBs may be used in patients who are intolerant to ACE inhibitors. Hydralazine and a nitrate may be used in patients intolerant to ACE inhibitors and ARBs, or

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Heart Failure Practice Guidelines (Executive Summary) (2010)[32]	in whom such therapy is contraindicated. • The combination of an ACE inhibitor and a β-blocker is recommended in all patients with a LVEF ≤40%. • The routine use of an ARB with a combination of an ACE inhibitor and β-blocker in patients who have had a MI and have left ventricular dysfunction is not recommended. • The addition of an ARB can be considered in patients with heart failure due to reduced LVEF who have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor and a β-blocker. • Individual ARBs may be considered as initial therapy (instead of an ACE inhibitor) in patients with heart failure who have had a MI and in patients with chronic heart failure and systolic dysfunction. • ARBs are recommended in patients who cannot tolerate ACE inhibitors due to cough. The combination of hydralazine and an oral nitrate may be considered in such patients not tolerating ARB therapy. • Patients intolerant to ACE inhibitors from hyperkalemia or renal insufficiency are likely to experience the same side effects with ARBs. In these cases, the combination of hydralazine and an oral nitrate should be considered. • ARBs should be considered in patients experiencing angioedema while on ACE inhibitors based on their underlying risk and with recognition that angioedema has been reported infrequently with ARBs. The combination of hydralazine and oral nitrates may be considered in such patients not tolerating ARB therapy. • A combination of hydralazine and an oral nitrate is recommended in African American patients with heart failure and reduced left ventricular ejection fraction (LVEF) who are on a standard regimen of an ACE inhibitor (or ARB) and a β-blocker. • A combination of hydralazine and an oral nitrate may be considered in non–African American patients with heart failure and reduced LVEF who are symptomatic despite optimization of standard therapy. • Administration of an aldosterone antagonist is recommended for patients with New York Heart Association (NYHA) class IV (or class III, previously class IV) heart failure from reduced LVEF (<35%) while receiving standard therapy, including diuretics. • Administration of an aldosterone antagonist should be considered in patients following an acute MI, with clinical heart failure signs and symptoms or history of diabetes mellitus, and an LVEF <40%. Patients should be on standard therapy, including an ACE inhibitor (or ARB) and a β-blocker. • The triple combination of an ACE inhibitor, an ARB, and an aldosterone antagonist is not recommended because of the high risk of hyperkalemia. <u>Patients with hypertension and symptomatic left ventricular dysfunction with left ventricular dilation and low LVEF</u> • ACE inhibitors, ARBs, β-blockers, aldosterone inhibitors, and isosorbide dinitrate/hydralazine in various combinations (with a loop diuretic if needed) are recommended. • If blood pressure remains >130/80 mm Hg, a dihydropyridine calcium channel blocker (e.g., amlodipine or felodipine) may be considered or other antihypertensive medication doses increased. <u>Managing heart failure in special populations</u> • The combination of hydralazine/isosorbide dinitrate is recommended for African American women with moderate to severe heart failure symptoms who are on background neurohormonal inhibition. • A combination of hydralazine and isosorbide dinitrate is recommended as part of standard therapy in addition to β-blockers and ACE-inhibitors for African

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	Americans with left ventricular systolic dysfunction and NYHA class II-IV heart failure. • As in all patients, but especially in the elderly, careful attention to volume status, the possibility of symptomatic cerebrovascular disease and the presence of postural hypotension are recommended during therapy with ACE inhibitors, β-blockers and diuretics. <u>Patients with heart failure and preserved LVEF</u> • ACE inhibitors or ARBs should be considered in this patient population. • ACE inhibitors should be considered in patients with heart failure and symptomatic atherosclerotic cardiovascular disease or diabetes and at least one other risk factor. ARBs may be used in patients who are intolerant to ACE inhibitors. • Beta-blocker treatment is recommended in patients with HF and preserved LVEF who have prior MI, hypertension, or AF. • Calcium channel blockers should be considered in patients with heart failure and preserved LVEF who have atrial fibrillation requiring ventricular rate control and intolerance to β-blockers (consider diltiazem or verapamil), symptom-limiting angina, or hypertension. • Diuretic therapy is recommended in all patients with heart failure and clinical evidence of volume overload, including those with preserved LVEF. • Treatment may begin with either a thiazide or loop diuretic. In more severe volume overload or if response to a thiazide is inadequate, treatment with a loop diuretic should be implemented. • Excessive diuresis, which may lead to orthostatic changes in blood pressure and worsening renal function, should be avoided. <u>Patients with heart failure and CAD</u> • Calcium channel blockers should be considered in patients who have angina despite optimization of β-blocker and nitrates. Amlodipine and felodipine are preferred in patients with decreased systolic function. <u>Patients with heart failure and hypertension</u> • Patients with left ventricular hypertrophy or left ventricular dysfunction without left ventricular dilation should be treated to a goal blood pressure of <130/80 mm Hg. Treatment with several drugs may be necessary, including an ACE inhibitor (or ARB), a diuretic and a β-blocker or calcium channel blocker. • Patients with asymptomatic left ventricular dysfunction and left ventricular dilation and a reduced ejection fraction should receive an ACE inhibitor and a β-blocker. If blood pressure remains elevated (>130/80 mm Hg), the addition of a diuretic is recommended, followed by a calcium channel blocker or other antihypertensive agent. • If blood pressure remains >130/80 mm Hg, then the addition of a thiazide diuretic is recommended, followed by a dihydropyridine calcium channel blocker (e.g., amlodipine or felodipine) or other antihypertensive drugs. <u>Patients at risk for development of heart failure</u> • ACE inhibitors are recommended in patients who are at risk for the development of heart failure including patients with CAD, peripheral vascular disease, stroke, diabetes and another major risk factor, and patients with diabetes who smoke and have microalbuminuria. <u>Patients with asymptomatic heart failure and reduced LVEF</u> • ACE inhibitors are recommended in asymptomatic patients with reduced LVEF (<40%).

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	• ARBs may be used in patients who are intolerant to ACE inhibitors. • Routine use of a combination of ACE inhibitors and ARBs is not recommended. • β-blocker therapy should be considered. <u>Patients with heart failure and ischemic heart disease</u> • ACE inhibitor therapy is recommended in all patients with either reduced or preserved LVEF after a MI. • Beta-blockers are recommended for the management of all patients with reduced LVEF or post-MI. • ACE inhibitor and β-blocker therapy should be initiated early (<48 hours) during hospitalization in hemodynamically stable patients who are post-MI with reduced LVEF or heart failure. • Calcium channel blockers may be considered in patients with HF who have angina despite the optimal use of β-blockers and nitrates. <u>Managing heart failure in the elderly, women and African Americans</u> • Standard regimens of ACE inhibitors and β-blockers are recommended in elderly patients with heart failure. • ACE inhibitor and β-blocker therapy are recommended in all women with heart failure and left ventricular systolic dysfunction. • ACE inhibitor and β-blocker therapy are recommended in all African American patients with heart failure and left ventricular systolic dysfunction. ARBs may be substituted in patients who are intolerant to ACE inhibitors. <u>Heart failure in patients with reduced ejection fraction</u> • ACE inhibitors are recommended in asymptomatic patients with reduced LVEF (<40%). • ARBs may be used in patients who are intolerant to ACE inhibitors. • β-blockers shown to be effective in clinical trials of patients with heart failure are recommended for patients with a LVEF ≤40%. • The combination of a β-blocker and an ACE inhibitor is recommended as routine therapy for asymptomatic patients with a LVEF ≤40%. The evidence is stronger in patients with a history of MI. • β-blocker therapy is recommended for patients with a recent decompensation of heart failure after optimization of volume status and successful discontinuation of intravenous diuretics and vasoactive drugs. Whenever possible, β-blocker therapy should be initiated in the hospital setting at a low dose prior to discharge of stable patients. • β-blocker therapy is recommended in the great majority of patients with heart failure and reduced LVEF, even if there is concurrent diabetes, chronic obstructive pulmonary disease or peripheral vascular disease. Caution may be warranted in these patients. • It is recommended that β blockade be initiated at low doses and uptitrated gradually. • It is recommended that β-blocker therapy be continued in most patients experiencing a symptomatic exacerbation of heart failure during chronic maintenance treatment, unless they develop cardiogenic shock, refractory volume overload or symptomatic bradycardia. • The routine use of an ARB is not recommended in addition to an ACE inhibitor and a β-blocker in patients with a recent acute MI and reduced LVEF. • The addition of an ARB should be considered in patients with heart failure due to reduced LVEF who have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor and a β-blocker. • Administration of an aldosterone antagonist is recommended for patients with NYHA class IV (or class III, previously class IV) HF from reduced LVEF

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	(<35%) while receiving standard therapy, including diuretics. • Diuretic therapy is recommended to restore and maintain normal volume status in patients with clinical evidence of fluid overload, generally manifested by congestive symptoms or signs of elevated filling pressures. Loop diuretics rather than thiazide-type diuretics are typically necessary to restore normal volume status in patients with heart failure. • The initial dose of diuretic may be increased as necessary to relieve congestion, and restoration of normal volume status may require multiple adjustments, especially in patients with severe fluid overload evidenced by massive edema or ascites. After a diuretic effect is achieved with loop diuretics (short acting), increasing administration frequency to twice or even three times/day will provide more diuresis with less physiologic perturbation than larger single doses. • Oral torsemide may be considered in patients in whom poor absorption of oral medication or erratic diuretic effect may be present. Particularly in patients with right-sided heart failure and refractory fluid retention despite high doses of other loop diuretics. • Intravenous administration of diuretics may be necessary to relieve congestion. • Diuretic refractoriness may represent patient nonadherence, a direct effect of diuretic use on the kidney or progression of underlying cardiac dysfunction. • Addition of chlorothiazide or metolazone, once or twice daily, to loop diuretics should be considered in patients with persistent fluid retention despite high dose loop diuretic therapy. Chronic daily use should be avoided if possible because of the potential for electrolyte shifts and volume depletion. These drugs may be used periodically (every other day or weekly) to optimize fluid management. Metolazone will generally be more potent and much longer acting in this setting and in patients with chronic renal insufficiency, so administration should be adjusted accordingly. Volume status and electrolytes must be monitored closely when multiple diuretics are used. • Careful observation for the development of side effects is recommended in patients treated with diuretics, especially when high doses or combination therapy are used. Patients should undergo routine laboratory studies and clinical examination as dictated by their clinical response. • Patients requiring diuretic therapy to treated fluid retention associated with heart failure generally require chronic treatment, although often at lower doses than those required initially to achieve diuresis. Decreasing or discontinuing therapy may be considered in patients experiencing significant improvement in clinical status and cardiac function or in those who successfully restrict dietary sodium intake. These patients may undergo cautious weaning of diuretic dose and frequency with careful observation for recurrent fluid retention. • Patients and caregivers should be given education on the early signs of fluid retention and the plan for initial therapy. • Selected patients may be educated to adjust daily dose of diuretic in response to weight gain from fluid overload. <u>Evaluation and management of patients with acute decompensated heart failure</u> • Patients admitted with acute decompensated heart failure and evidence of fluid overload be treated initially with loop diuretics; usually given intravenously rather than orally. Ultrafiltration may be considered in lieu of diuretics. • Diuretics should be administered at doses needed to produce a rate of diuresis sufficient to achieve optimal volume status with relief of signs and symptoms of congestion, without inducing an excessively rapid reduction in intravascular volume or serum electrolytes. • Monitoring of daily weights, intake and output is recommended to assess clinical efficacy of diuretic therapy. • Careful observation for development of a variety of side effects, including renal

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	dysfunction, electrolyte abnormalities, symptomatic hypotension and gout is recommended in patients treated with diuretics, especially when high doses or combination therapy is used.
	• Careful observation for the development of renal dysfunction is recommended in patients treated with diuretics. Patients with moderate to severe renal dysfunction and evidence of fluid retention should continue to be treated with diuretics. In the presence of severe fluid overload, renal dysfunction may improve with diuresis.
	• When congestion fails to improve in response to diuretic therapy, the following options should be considered:
	  ○ Re-evaluating the presence/absence of congestion.
	  ○ Sodium and fluid restriction.
	  ○ Increasing doses of loop diuretic.
	  ○ Continuous infusion of a loop diuretic.
	  ○ Addition of a second type of diuretic orally (metolazone or spironolactone) or intravenously (chlorothiazide).
	  ○ Ultrafiltration may be considered as well.

European Society of Cardiology: **Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (2016)**[33]	Pharmacological treatments indicated in patients with symptomatic (NYHA Class II-IV) heart failure with reduced ejection fraction • An ACE inhibitor is recommended, in addition to a beat-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death. • A mineralocorticoid receptor antagonist 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. • Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion. • 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. • 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. • 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

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	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 heart failure with preserved ejection fraction and heart failure with mid-range ejection fraction</u> • It is recommended to screen patients with HFpEF or HFmrEF (mid-range) 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 or HFmrEF in order to alleviate symptoms and signs. <u>Recommendations for initial management of a rapid ventricular rate in patients with heart failure and atrial fibrillation in the acute or chronic setting</u> • Urgent electrical cardioversion is recommended if AF is thought to be contributing to the patient's hemodynamic compromise in order to improve the patient clinical condition. • For patients in NYHA Class IV, in addition to treatment for acute HF, an intravenous bolus of amiodarone or, in digoxin-naïve patients, an intravenous bolus of digoxin should be considered to reduce the ventricular rate. • For patients in NYHA Class I–III, a β-blocker, usually given orally, is safe and therefore is recommended as first-line treatment to control ventricular rate, provided the patient is euvolemic. • For patients in NYHA Class I–III, digoxin should be considered when ventricular rate remains high despite β-blockers or when β-blockers are not tolerated or contraindicated. • Treatment with dronedarone to improve ventricular rate control is not recommended due to safety concerns. <u>Recommendations for cardiac imaging in patients with suspected or established heart failure</u> • Transthoracic Echocardiogram (TTE) is recommended for the assessment of myocardial structure and function in subjects with suspected HF in order to establish a diagnosis of HFrEF, HFmrEF, or HFpEF. • TTE is recommended for the assessment of LVEF in order to identify patients with HF who would be suitable for evidence-based pharmacological and device treatment recommended for HFrEF. <u>Recommendations aiming to prevent or delay the development of overt heart failure or prevent death before the onset of symptoms</u> • Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life. • ACE inhibitor is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction in order to prevent or delay the onset of HF and prolong life. • β-blocker is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction, in order to prevent or delay the onset of HF and prolong life. <u>Pharmacological treatments indicated in patients with symptomatic heart failure with reduced ejection fraction</u> • An ACE inhibitor is recommended, in addition to a β-blocker, for symptomatic

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	patients with HFrEF to reduce the risk of HF hospitalization and death. • A β-blocker is recommended, in addition to an ACE inhibitor, for patients with stable, symptomatic HFrEF to reduce the risk of HF hospitalization and death. • A mineralocorticoid receptor antagonist 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. Other pharmacological treatments recommended in selected patients with symptomatic heart failure with reduced ejection fraction • Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion. • 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. Treatments (or combinations of treatments) that may cause harm in patients with symptomatic (New York Heart Association Class II–IV) heart failure with reduced ejection fraction • Diltiazem or verapamil are not recommended in patients with HFrEF, as they increase the risk of HF worsening and HF hospitalization. • The addition of an ARB (or a renin inhibitor) to the combination of an ACE inhibitor and a mineralocorticoid receptor antagonist is not recommended in patients with HF, because of the increased risk of renal dysfunction and hyperkalemia. Not-recommended treatments of co-morbidities in patients with heart failure • Thiazolidinediones (glitazones) are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization. • NSAIDs or COX-2 inhibitors are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization. Recommendations for the 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. • In patients with new-onset AHF or those with chronic, decompensated HF not receiving oral diuretics the initial recommended dose should be 20 to 40 mg intravenous furosemide (or equivalent); for those on chronic diuretic therapy, initial intravenous dose should be at least equivalent to oral dose. • It is recommended to give diuretics either as intermittent boluses or a continuous infusion, and the dose and duration should be adjusted according to the patients' symptoms and clinical status. • Inotropic agents are not recommended unless the patient is symptomatically hypotensive or hypoperfused because of safety concern.
Eighth Joint National Committee (JNC 8): **2014 Evidence-based Guideline for the Management of High Blood Pressure in Adults**	• 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

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(2014)[34]	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.
American Society of Hypertension/ International Society of Hypertension: **Clinical Practice Guidelines for the Management of Hypertension in the Community (2014)[35]**	Nonpharmacologic treatment • In patients with hypertension that is no more severe than stage one and is not associated with evidence of abnormal cardiovascular findings or other cardiovascular risks, six to 12 months of lifestyle changes can be attempted in the hope that they may be sufficiently effective to make it unnecessary to use medicines. • It may be prudent to start treatment with drugs sooner if it is clear that the blood pressure is not responding to the lifestyle methods or if other risk factors appear. • Weight loss: In patients who are overweight or obese, weight loss is helpful in treating hypertension, diabetes, and lipid disorders. • Salt reduction: Reduction of salt intake is recommended because it can reduce blood pressure and decrease the need for medications in patients who are "salt sensitive." • Exercise: Regular aerobic exercise can help reduce blood pressure. • Alcohol consumption: Up to two drinks a day can be helpful in protecting against cardiovascular events, but greater amounts of alcohol can raise blood pressure and should therefore be discouraged. In women, alcohol should be limited to one drink a day. • Cigarette smoking: Stopping smoking will not reduce blood pressure, but since smoking by itself is such a major cardiovascular risk factor, patients must be strongly urged to discontinue this habit. Drug treatment of hypertension • Treatment with drugs should be started in patients with blood pressures >140/90 mm Hg in whom lifestyle treatments have not been effective.

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	• In patients with stage two hypertension (blood pressure ≥160/100 mm Hg), drug treatment should be started immediately after diagnosis, usually with a two-drug combination, without waiting to see the effects of lifestyle changes.
	• For patients older than 80 years, the suggested threshold for starting treatment is at levels ≥150/90 mm Hg. Thus, the target of treatment should be <140/90 mm Hg for most patients but <150/90 mm Hg for older patients (unless these patients have chronic kidney disease or diabetes, when <140/90 mm Hg can be considered).
	• Most patients will require more than one drug to achieve control of their blood pressure.
	• In general, increase the dose of drugs or add new drugs at approximately two to three week intervals. This frequency can be faster or slower depending on the judgment of the practitioner. In general, the initial doses of drugs chosen should be at least half of the maximum dose so that only one dose adjustment is required thereafter. It is generally anticipated that most patients should reach an effective treatment regimen, whether one, two, or three drugs, within six to eight weeks.
	• Choice of drugs should be influenced by the age, ethnicity/race, and other clinical characteristics of the patient.
	• The choice of drugs will also be influenced by other conditions (e.g., diabetes and coronary disease) associated with the hypertension. Pregnancy also influences drug choice.
	• Long-acting drugs that need to be taken only once daily are preferred to shorter-acting drugs that require multiple doses because patients are more likely to follow a simple treatment regimen.
	• This guideline only makes recommendations for drug classes, not individual agents. There is an assumption, unless otherwise stated, that all drugs in a class are similar to each other.
	• Drug selectin when hypertension is the only or main concern:
	  ○ For black patients of all ages, use calcium channel blocker (CCB) or thiazide diuretic as first drug, then add angiotensin receptor blocker (ARB) or angiotensin-converting enzyme (ACE) inhibitor if needed.
	  ○ For white and other non-black patients <60 years of age, use ARB or ACE inhibitor as first drug, then add CCB or thiazide diuretic if needed.
	  ○ For white and other non-black patients ≥60 years of age, use CCB or thiazide diuretic as first drug, then add ARB or ACE inhibitor if needed.
	• Drug selection when hypertension is associated with other conditions:
	  ○ For patients with hypertension and diabetes, use ARB or ACE inhibitor as first drug (note, in black patients it is acceptable to start with a CCB or thiazide), then add CCB or thiazide diuretic (unless starting on CCB or thiazide in black patients) if needed.
	  ○ For patients with hypertension and chronic kidney disease, use ARB or ACE inhibitor as first drug, then add CCB or thiazide diuretic if needed.
	  ○ For patients with hypertension and clinical coronary artery disease, use β-blocker plus ARB or ACE inhibitor as first drugs, then add CCB or thiazide diuretic if needed.
	  ○ For patients with hypertension and stroke history, use ACE inhibitor or ARB as first drug, then add thiazide diuretic or CCB if needed.
	• For patients with hypertension and heart failure, patients with h symptomatic heart failure should usually receive an ARB or ACE inhibitor plus β-blocker plus diuretic plus spironolactone regardless of blood pressure. A dihydropyridine CCB can be added if needed for blood pressure control.

Hypertension Canada: **2017 Guidelines for Diagnosis, Risk Assessment,**	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

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Prevention, and Treatment of Hypertension in Adults (2017)[36]	(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.
	
	<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>Guidelines for individuals 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

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	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. Treatment of hypertension in association with stroke • BP management in acute ischemic stroke (onset to 72 hours) ○ For patients with ischemic stroke not eligible for thrombolytic therapy, treatment of hypertension in the setting of acute ischemic stroke or transient

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	ischemic attack should not be routinely undertaken. Extreme BP increases (e.g., SBP >220 mmHg or DBP >120 mmHg) may be treated to reduce the BP by approximately 15%, and not more than 25%, over the first 24 hours with gradual reduction thereafter. Avoid excessive lowering of BP because this might exacerbate existing ischemia or might induce ischemia, particularly in the setting of intracranial arterial occlusion or extracranial carotid or vertebral artery occlusion. Pharmacological agents and routes of administration should be chosen to avoid precipitous decreases in BP. ○ For patients with ischemic stroke eligible for thrombolytic therapy, very high BP (>185/110 mmHg) should be treated concurrently in patients receiving thrombolytic therapy for acute ischemic stroke to reduce the risk of secondary intracranial hemorrhage. • 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) ○ For patients with intracerebral hemorrhage (ICH) in the hyperacute phase (in the first 24 hours) SBP lowering to <140 mmHg should be avoided because of an absence of benefit (relative to a target of <180 mmHg) and some suggestion of harm. <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> • For patients with nondiabetic chronic kidney disease, target BP is <140/90 mmHg. • For patients with hypertension and proteinuric chronic kidney disease (urinary protein >500 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. • Thiazide/thiazide-like diuretics are recommended as additive antihypertensive therapy. For patients with chronic kidney disease and volume overload, loop diuretics are an alternative. • 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

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	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. • In patients with hypertension attributable to FMD-related renal artery stenosis, revascularization should be considered. • 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 2 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. Combination therapy using two first-line agents may also be considered as initial treatment of hypertension if SBP is 20 mmHg greater than target or if DBP is 10 mmHg greater than target. However, caution should be exercised in patients in whom a substantial decrease in BP is more likely or poorly tolerated (e.g., elderly patients and patients with autonomic neuropathy). • 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.
European Society of Hypertension/ European Society of Cardiology: **2013 Guidelines for the management of arterial hypertension (2013)**[37]	The 2013 guidelines on hypertension of the European Society of Hypertension and the European Society of Cardiology follow the guidelines jointly issued by the two societies in 2003 and 2007. <u>Treatment strategies and choice of antihypertensive drugs</u> • Diuretics (including thiazides, chlorthalidone, and indapamide), β-blockers, calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) are all suitable for the initiation and maintenance of antihypertensive treatment, either as monotherapy or in some combinations. • Some agents should be considered as the preferential choice in specific conditions because used in trials in those conditions or because of greater effectiveness in specific types of organ damage. • Initiation of antihypertensive therapy with a two-drug combination may be considered in patients with markedly high baseline blood pressure (BP) or at high cardiovascular (CV) risk. • The combination of two antagonists of the renin-angiotensin system (RAS) is not recommended and should be discouraged. • Other drug combinations should be considered and probably are beneficial in proportion to the extent of BP reduction. However, combinations that have been successfully used in trials may be preferable. • Combinations of two antihypertensive drugs at fixed doses in a single tablet may be recommended and favored, because reducing the number of daily pills improves adherence, which is low in patients with hypertension. <u>Treatment strategies in white-coat and masked hypertension</u>

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	• In white-coat hypertensives without additional risk factors, therapeutic intervention may be limited to lifestyle changes only, but this decision should be accompanied by close follow-up. • In white-coat hypertensives with a higher CV risk because of metabolic derangements or asymptomatic organ damage, drug treatment may be considered in addition to lifestyle changes. • In masked hypertension, both lifestyle measures and antihypertensive drug treatment should be considered, because this type of hypertension has been consistently found to have a CV risk very close to that of in- and out-of-office hypertension. <u>Antihypertensive treatment strategies in the elderly</u> • In elderly hypertensives with SBP ≥160 mmHg there is solid evidence to recommend reducing SBP to between 150 and 140 mmHg. • In fit elderly patients <80 years old antihypertensive treatment may be considered at SBP values ≥140 mmHg with a target SBP <140 mmHg if treatment is well tolerated. • In individuals older than 80 years with an initial SBP ≥160 mmHg, it is recommended to reduce SBP to between 150 and 140 mmHg, provided they are in good physical and mental conditions. • In frail elderly patients, it is recommended to leave decisions on antihypertensive therapy to the treating physician, and based on monitoring of the clinical effects of treatment. • Continuation of well-tolerated antihypertensive treatment should be considered when a treated individual becomes octogenarian. • All hypertensive agents are recommended and can be used in the elderly, although diuretics and calcium antagonists may be preferred in isolated systolic hypertension. <u>Treatment strategies in hypertensive women</u> • Hormone therapy and selective estrogen receptor modulators are not recommended and should not be used for primary or secondary prevention of CVD. • If treatment of younger perimenopausal women is considered for severe menopausal symptoms, the benefits should be weighed against potential risks. • Drug treatment of severe hypertension in pregnancy (SBP >160 mmHg or DBP >110 mmHg) is recommended. • Drug treatment may also be considered in pregnant women with persistent elevation of BP ≥150/95 mmHg, and in those with BP ≥140/90 mmHg in the presence of gestational hypertension, subclinical organ damage or symptoms. • In women at high risk of pre-eclampsia, provided they are at low risk of gastrointestinal hemorrhage, treatment with low dose aspirin from 12 weeks until delivery may be considered. • In women with child-bearing potential RAS blockers are not recommended and should be avoided. • Methyldopa, labetalol, and nifedipine should be considered preferential antihypertensive drugs in pregnancy. Intravenous labetalol or infusion of nitroprusside should be considered in case of emergency (pre-eclampsia). <u>Treatment strategies in patients with diabetes</u> • While initiation of antihypertensive drug treatment in diabetic patients whose SBP is ≥160 mmHg is mandatory, it is strongly recommended to start drug treatment also when SBP is ≥140 mmHg. • A SBP goal <140 mmHg is recommended in patients with diabetes. • The DBP target in patients with diabetes is recommended to be <85 mmHg.

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	• All classes of antihypertensive agents are recommended and can be used in patients with diabetes; RAS blockers may be preferred, especially in the presence of proteinuria or microalbuminuria. • It is recommended that individual drug choice takes comorbidities into account. • Simultaneous administration of two blockers of the RAS is not recommended and should be avoided in patients with diabetes <u>Treatment strategies in hypertensive patients with metabolic syndrome</u> • Lifestyle changes, particularly weight loss and physical exercise, are to be recommended to all individuals with the metabolic syndrome. These interventions improve not only BP, but the metabolic components of the syndrome and delay diabetes onset. • As the metabolic syndrome can be considered a 'pre-diabetic' state, antihypertensive agents potentially improving or at least not worsening insulin sensitivity, such as RAS blockers and calcium antagonists, should be considered as the preferred drugs. Beta-blockers (with the exception of vasodilating β-blockers) and diuretics should be considered only as additional drugs, preferably in association with a potassium-sparing agent. • It is recommended to prescribe antihypertensive drugs with particular care in hypertensive patients with metabolic disturbances when BP is ≥140/90 mmHg after a suitable period of lifestyle changes, and to maintain BP <140/90 mmHg. • BP lowering drugs are not recommended in individuals with metabolic syndrome and high normal BP. <u>Therapeutic strategies in hypertensive patients with nephropathy</u> • Lowering SBP to <140 mmHg should be considered. • When overt proteinuria is present, SBP values <130 mmHg may be considered, provided that changes in eGFR are monitored. • RAS blockers are more effective in reducing albuminuria than other antihypertensive agents, and are indicated in hypertensive patients in the presence of microalbuminuria or overt proteinuria. • Reaching BP goals usually requires combination therapy, and it is recommended to combine RAS blockers with other antihypertensive agents. • Combination of two RAS blockers, though potentially more effective in reducing proteinuria, is not recommended. • Aldosterone antagonists cannot be recommended in chronic kidney disease (CKD), especially in combination with a RAS blocker, because of the risk of excessive reduction in renal function and of hyperkalemia. <u>Therapeutic strategies in hypertensive patients with cerebrovascular disease</u> • It is not recommended to intervene with BP-lowering therapy during the first week after acute stroke irrespective of BP level, although clinical judgement should be used in the face of very high SBP values. • Antihypertensive treatment is recommended in hypertensive patients with a history of stroke or transient ischemic attack (TIA), even when initial SBP is in the 140 to 159 mmHg range. • In hypertensive patients with a history of stroke or TIA, a SBP goal of <140 mmHg should be considered. • In elderly hypertensives with previous stroke or TIA, SBP values for intervention and goal may be considered to be somewhat higher. • All drug regimens are recommended for stroke prevention, provided that BP is effectively reduced. <u>Therapeutic strategies in hypertensive patients with heart disease</u> • In hypertensive patients with CHD, a SBP goal <140 mmHg should be

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	considered. • In hypertensive patients with a recent myocardial infarction, β-blockers are recommended. In case of other CHD all antihypertensive agents can be used, but β-blockers and calcium antagonists are to be preferred for symptomatic reasons (angina). • Diuretics, β-blockers, ACE inhibitors, angiotensin receptor blockers, and/or mineralocorticoid receptor antagonists are recommended in patients with heart failure or severe left ventricular (LV) dysfunction to reduce mortality and hospitalization. • In patients with heart failure and preserved ejection fraction (EF), there is no evidence that antihypertensive therapy per se or any particular drug is beneficial. However, in these patients, as well as in patients with hypertension and systolic dysfunction, lowering SBP to around 140 mmHg should be considered. Treatment guided by relief of symptoms (congestion with diuretics, high heart rate with β-blockers, etc.) should also be considered. • ACE inhibitors and angiotensin receptor blockers (and β-blockers and mineralocorticoid receptor antagonists if heart failure coexists) should be considered as antihypertensive agents in patients at risk of new or recurrent atrial fibrillation. • It is recommended that all patients with left ventricular hypertrophy (LVH) receive antihypertensive agents. • In patients with LVH, initiation of treatment with one of the agents that have shown a greater ability to regress LVH should be considered, i.e. ACE inhibitors, angiotensin receptor blockers, and calcium antagonists. <u>Therapeutic strategies in hypertensive patients with atherosclerosis, arteriosclerosis, and peripheral artery disease (PAD)</u> • In the presence of carotid atherosclerosis, prescription of calcium antagonists and ACE inhibitors should be considered as these agents have shown a greater efficacy in delaying atherosclerosis progression than diuretics and β-blockers. • In hypertensive patients with a pulse wave velocity above 10 m/s, all antihypertensive drugs should be considered provided that a BP reduction to <140/90 mmHg is consistently achieved. • Antihypertensive therapy is recommended in hypertensive patients with PAD to achieve a goal of <140/90 mmHg, because of their high risk of myocardial infarction, stroke, heart failure, and CV death. • Though a careful follow up is necessary, β-blockers may be considered for the treatment of arterial hypertension in patients with PAD, since their use does not appear to be associated with exacerbation of PAD symptoms.
National Institute for Health and Clinical Excellence: **Hypertension in adults: diagnosis and management (2011)**[38] **Reaffirmed Nov 2016**	<u>Choosing antihypertensive drug treatment</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 people ≥80 years of age the same antihypertensive drug treatment as people aged 55 to 80 years, taking into account any comorbidities. • Offer antihypertensive drug treatment to women of child-bearing potential in line with the recommendations on Management of pregnancy with chronic hypertension and Breastfeeding in 'Hypertension in pregnancy' (NICE clinical guideline 107). <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

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	(ARB). 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 step one antihypertensive (ACE inhibitor, ARB) with a calcium channel blocker (CCB) to patients >55 years of age and to black patients of African or Caribbean family origin 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 chlorthalidone (12.5 to 25.0 mg once daily) or indapamide (1.5 mg modified-release once daily or 2.5 mg once daily) in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide.
	• For patients who are already receiving treatment with bendroflumethiazide or hydrochlorothiazide and whose blood pressure is stable and well controlled, continue treatment as is.
	• β-blockers are not a preferred initial therapy for hypertension; however, β-blockers may be considered in younger patients, particularly:
	  ○ Patients with an intolerance or contraindication to ACE inhibitors and ARBs.
	  ○ Women of child-bearing potential.
	  ○ People with evidence of increased sympathetic drive.
	• If treatment is initiated with a β-blocker and a second antihypertensive is required, add a CCB over a thiazide-like diuretic to reduce the risk of developing diabetes.
	
	<u>Step two treatment</u>
	• If blood pressure is not controlled with a step one antihypertensive, offer a step two treatment with a CCB in combination with an ACE inhibitor or an ARB.
	• If a CCB is not appropriate or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic.
	• For black patients of African or Caribbean family origin, consider an ARB in preference to an ACE inhibitor, in combination with a CCB.
	
	<u>Step three treatment</u>
	• Before considering step three treatment, review medication to ensure step two treatment is at optimal or best tolerated doses.
	• If three drugs are required to control blood pressure, the combination of an ACE inhibitor or ARB, CCB, and thiazide-like diuretic should be utilized.
	
	<u>Step four treatment</u>
	• Regard clinic blood pressure that remains >140/90 mmHg after treatment with the optimal or best tolerated doses of an ACE inhibitor or an ARB plus a CCB plus a diuretic as resistant hypertension, and consider adding a fourth antihypertensive drug and/or seeking expert advice.
	• For treatment of resistant hypertension at step four:
	  ○ Consider further diuretic therapy with low-dose spironolactone (25 mg once daily) if the blood potassium level is 4.5 mmol/l or lower. Use particular caution in people with a reduced estimated glomerular filtration rate because they have an increased risk of hyperkalemia.
	  ○ Consider higher-dose thiazide-like diuretic treatment if the blood potassium level is higher than 4.5 mmol/l.
	• If further diuretic therapy for resistant hypertension is not tolerated or is contraindicated or ineffective, consider an α-blocker or β-blocker.

International Society on Hypertension in	• To attain and maintain blood pressure (BP) below target levels, multiple antihypertensive drugs will be required in most hypertensive blacks.

Clinical Guideline	Recommendations
Blacks: **Management of High Blood Pressure in Blacks (2010)[39]**	• 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 (2012)[40]**	<u>Blood pressure management in chronic kidney disease (CKD) non-dialysis (ND) patients without diabetes mellitus</u> • The Work Group recommends that non-diabetic adults with CKD ND and urine albumin excretion <30 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >140 mm Hg systolic or >90 mm Hg diastolic be treated with blood pressure -lowering drugs to maintain a blood pressure that is consistently ≤140 mm Hg systolic and ≤90 mm Hg diastolic. • The Work Group suggests that non-diabetic adults with CKD ND and urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with BP-lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic. • The Work Group suggests that non-diabetic adults with CKD ND and urine albumin excretion >300 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with blood pressure -lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤ 80 mm Hg diastolic. • The Work Group suggests that an angiotensin receptor blocker (ARB) or angiotensin converting enzyme inhibitor (ACE-I) be used in non-diabetic adults with CKD ND and urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*) in whom treatment with blood pressure -lowering drugs is indicated. • The Work Group recommends that an ARB or ACE-I be used in non-diabetic adults with CKD ND and urine albumin excretion >300 mg per 24 hours (or equivalent*) in whom treatment with blood pressure -lowering drugs is indicated. <u>Blood pressure management in CKD ND patients with diabetes mellitus</u> • The Work Group recommends that adults with diabetes and CKD ND with urine albumin excretion <30 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >140 mm Hg systolic or >90 mm Hg diastolic be treated with BP-lowering drugs to maintain a blood pressure that is consistently ≤140 mm Hg systolic and ≤90 mm Hg diastolic. • The Work Group suggests that adults with diabetes and CKD ND with urine albumin excretion >30 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated

Clinical Guideline	Recommendations
	with BP-lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic. • The Work Group suggests that an ARB or ACE-I be used in adults with diabetes and CKD ND with urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*). • The Work Group recommends that an ARB or ACE-I be used in adults with diabetes and CKD ND with urine albumin excretion >300 mg per 24 hours (or equivalent*). <u>Blood pressure management in kidney transplant recipients (non–dialysis-dependent CKD of any stage with a kidney transplant [CKD T])</u> • The Work Group suggests that adult kidney transplant recipients whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic, irrespective of the level of urine albumin excretion. • In adult kidney transplant recipients, choose a blood pressure -lowering agent after taking into account the time after transplantation, use of calcineurin inhibitors, presence or absence of persistent albuminuria, and other co morbid conditions. <u>Blood pressure management in children with CKD ND</u> • The Work Group recommends that in children with CKD ND, blood pressure -lowering treatment is started when blood pressure is consistently above the 90th percentile for age, sex, and height. • The Work Group suggests that in children with CKD ND (particularly those with proteinuria), blood pressure is lowered to consistently achieve systolic and diastolic readings less than or equal to the 50th percentile for age, sex, and height, unless achieving these targets is limited by signs or symptoms of hypotension. • The Work Group suggests that an ARB or ACE-I be used in children with CKD ND in whom treatment with blood pressure -lowering drugs is indicated, irrespective of the level of proteinuria. <u>Blood pressure management in elderly persons with CKD ND</u> • Tailor blood pressure treatment regimens in elderly patients with CKD ND by carefully considering age, co-morbidities and other therapies, with gradual escalation of treatment and close attention to adverse events related to blood pressure treatment, including electrolyte disorders, acute deterioration in kidney function, orthostatic hypotension and drug side effects. *Approximate equivalents for albumin excretion rate per 24 hours is expressed as protein excretion rate per 24 hours, albumin/creatinine ratio, protein/creatinine ratio, and protein reagent strip results.
American Diabetes Association: **Standards of Medical Care in Diabetes (2017)**[41]	<u>Hypertension/blood pressure control</u> • Blood pressure should be measured at every routine visit. Patients found to have elevated blood pressure should have blood pressure confirmed on a separate day. • Most patients with diabetes and hypertension should be treated to a systolic blood pressure goal of <140 mmHg and a diastolic blood pressure goal of <90 mmHg. • Lower systolic and diastolic blood pressure targets, such as 130/80 mmHg, may be appropriate for individuals at high risk of cardiovascular disease, if they can be achieved without undue treatment burden. • In pregnant patients with diabetes and chronic hypertension, blood pressure targets of 120 to 160/80 to 105 mmHg are suggested in the interest of optimizing long-term maternal health and minimizing impaired fetal growth. • Patients with confirmed office-based blood pressure >140/90 mmHg should, in

Clinical Guideline	Recommendations
	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). 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. • For patients with blood pressure >120/80 mmHg, lifestyle intervention consists of weight loss if overweight or obese; a Dietary Approaches to Stop Hypertension–style dietary pattern including reducing sodium and increasing potassium intake; moderation of alcohol intake; and increased physical activity. <u>Coronary heart disease</u> • In asymptomatic patients, routine screening for coronary artery disease is not recommended as it does not improve outcomes as long as atherosclerotic cardiovascular disease risk factors are treated. • Consider investigations for coronary artery disease in the presence of any of the following: atypical cardiac symptoms (e.g., unexplained dyspnea, chest discomfort); signs or symptoms of associated vascular disease including carotid bruits, transient ischemic attack, stroke, claudication, or peripheral arterial disease; or electrocardiogram abnormalities (e.g., Q waves). • In patients with known atherosclerotic cardiovascular disease, use aspirin and statin therapy (if not contraindicated) and consider ACE inhibitor therapy to reduce the risk of cardiovascular events. • In patients with prior myocardial infarction, β-blockers should be continued for at least two years after the event. • In patients with symptomatic heart failure, thiazolidinedione treatment should not be used. • In patients with type 2 diabetes with stable congestive heart failure, metformin may be used if estimated glomerular filtration remains >30 mL/min but should be avoided in unstable or hospitalized patients with congestive heart failure. <u>Diabetic 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, in all patients with type 2 diabetes, and in all patients with comorbid hypertension. • Optimize glucose control to reduce the risk or slow the progression of diabetic kidney disease. • Optimize blood pressure control to reduce the risk or slow the progression of diabetic kidney disease. • For people with nondialysis-dependent diabetic kidney disease, dietary protein

Clinical Guideline	Recommendations
	intake should be approximately 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. • 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) B 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 or changes in potassium when ACE inhibitors, angiotensin receptor blockers, or diuretics are used. • Continued monitoring of urinary albumin–to–creatinine ratio in patients with albuminuria treated with an ACE inhibitor or an angiotensin receptor blocker is reasonable to assess the response to treatment and progression of diabetic kidney disease. • An ACE inhibitor or an angiotensin receptor blocker is not recommended for the primary prevention of diabetic kidney disease 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. • When estimated glomerular filtration rate is <60 mL/min/1.73 m^2, evaluate and manage potential complications of chronic kidney disease. • Patients should be referred for evaluation for renal replacement treatment if they have an estimated glomerular filtration rate <30 mL/min/1.73 m^2. • Promptly refer to a physician experienced in the care of kidney disease 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 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 upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Angiotensin II Receptor Antagonists-Single Entity Agents[3-21]

Indication(s)	Single Entity Agents							
	Azil-sartan	Cande-sartan	Epro-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[3-21]

Indication(s)	Combination Products									
	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	Valsartan and Nebivolol
Cardiovascular Risk Reduction										
Reduce the risk of stroke in patients				✔ *						

Indication(s)	Combination Products									
	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**	**Valsartan and Nebivolol**
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[22]

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
Eprosartan	13	98	Liver (20)	Feces (90) Renal (7)	5 to 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)/	Feces (83) Renal (13)/	6 to 9/ 10 to 12

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
			Not reported	Renal (70)	
Valsartan and nebivolol	25/12	95/98	Liver, minimal (% not reported)/ Liver, extensive (% not reported)	Feces (83) Renal (13)/ Feces (44) Renal (38)	6 to 9/ 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[22]

Generic Name(s)	Interaction	Mechanism
ARBs (azilsartan, candesartan, eprosartan, 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, eprosartan, 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, eprosartan, 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, eprosartan, 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

Generic Name(s)	Interaction	Mechanism
		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[3-21]

Adverse Events	Single Entity Agents							
	Azilsartan	Candesartan	Eprosartan	Irbesartan	Losartan	Olmesartan	Telmisartan	Valsartan
Cardiovascular								
Chest pain	-	>1	≥1	≥1	≥1	>0.5	1	-
Hypertension	-	-	-	<1	-	-	-	-
Hypotension	-	-	<1	<1	<1	-	-	<1
Orthostatic hypotension	-	-	✔	✔	-	-	-	-
Tachycardia	-	≥0.5	<1	≥1	<1	>0.5	>0.3	-
Central Nervous System								
Anxiety/nervousness	-	≥0.5	<1	≥1	<1	-	>0.3	>0.2
Depression	-	≥0.5	1	<1	<1	-	>0.3	-
Dizziness	≥0.3	4	≥1	≥1	4	3	1	>1
Dizziness, postural	≥0.3	-	-	-	-	-	-	-
Fatigue	-	>1	2	4	-	>0.5	1	2
Headache	-	≥1	≥1	≥1	≥1	>1	1	>1
Insomnia	-	-	<1	-	1	>0.5	>0.3	>0.2
Dermatological								
Rash	-	≥0.5	<1	≥1	<1	>0.5	>0.3	>0.2
Gastrointestinal								
Abdominal pain	-	>1	2	≥1	≥1	>0.5	1	2
Diarrhea	2	>1	≥1	3	2	>1	3	>1
Dyspepsia/heartburn	-	≥0.5	≥1	2	1	>0.5	1	>0.2
Nausea/vomiting	≥0.3	>1	<1	≥1	≥1	>0.5	1	>1
Genitourinary								
Albuminuria	-	>1	<1	-	-	-	-	-
Hematuria	-	≥0.5	<1	-	-	>1	-	-
Urinary tract infection	-	-	4	≥1	<1	>0.5	1	-
Laboratory Test Abnormalities								
Creatine phosphokinase increased	-	≥0.5	<1	-	-	>1	-	-
Decreased hematocrit	0.4	-	-	-	-	-	-	-
Decreased hemoglobin	0.2	-	-	-	-	-	-	-
Decreased red blood counts	0.3	-	-	-	-	-	-	-
Hyperglycemia	-	≥0.5	<1	-	-	>1	-	-
Hyperkalemia	-	✔	-	✔	✔	-	-	✔
Hypertriglyceridemia	-	≥0.5	1	-	-	>1	-	-
Hypokalemia	-	-	✔	-	-	-	-	-
Musculoskeletal								
Arthralgia	-	>1	2	-	<1	>0.5	>0.3	>1
Muscle cramp	-	-	-	-	1.1	-	-	>0.2
Muscle spasm	≥0.3	-	-	-	-	-	-	-

Adverse Events	Single Entity Agents							
	Azilsartan	Candesartan	Eprosartan	Irbesartan	Losartan	Olmesartan	Telmisartan	Valsartan
Myalgia	-	≥0.5	≥1	-	1	>0.5	1	>0.2
Pain (includes back and leg)	-	3	<1	≥1	1 to 2	>1	1 to 3	>0.2
Trauma	-	-	-	2	-	-	-	-
Respiratory								
Bronchitis	-	>1	≥1	-	<1	>1	>0.3	-
Cough	≥0.3	>1	4	3	3	-	1	>1
Influenza/influenza-like symptoms	-	-	<1	≥1	<1	>1	1	-
Nasal congestion	-	-	-	-	2	-	-	-
Pharyngitis	-	2	4	≥1	≥1	>1	1	>1
Rhinitis	-	2	4	≥1	<1	>1	>0.3	>1
Sinus disorder	-	-	-	≥1	2	-	-	-
Sinusitis	-	>1	≥1	-	1	>1	3	>1
Upper respiratory tract infection	-	6	8	9	8	>1	7	>1
Miscellaneous								
Allergic reactions	-	✔	✔	✔	✔	✔	✔	✔
Angioedema	-	✔	✔	✔	✔	✔	✔	✔
Asthenia	≥0.3	-	-	-	-	-	-	-
Edema	-	>1	≥1	≥1	≥1	>0.5	1	>1
Fatigue	≥0.3	-	-	-	-	-	-	-
Inflicted injury	-	-	2	-	-	>1	-	-
Viral infection	-	-	2	-	-	-	-	3

✔ Percent not specified
- Event not reported

Table 8. Adverse Drug Events (%) Reported with the Combination Angiotensin II Receptor Antagonists-Combination Products[3-21]

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	Valsartan and Nebivolol
Cardiovascular										
Abnormal electrocardiogram	-	≥0.5	-	-	-	-	-	-	-	-
Angina	-	<0.5	-	-	-	-	-	-	-	-
Arterial/vascular insufficiency	-	-	-	-	-	-	-	-	-	<1
Bradycardia	-	≥0.5	-	-	-	-	-	-	-	≤1
Chest pain	-	≥0.5	2	-	-	>1	-	-	>0.2	≤1
Extrasystoles	-	≥0.5	-	-	-	-	-	-	-	-
Hypotension	1.7	-	0.6 to 0.9	0.6	-	-	<2.0	<2	>0.2 to 1.0	<1
Myocardial infarction	-	<0.5	-	-	-	-	-	-	-	-
Palpitations	-	≥0.5	-	1.4	-	-	-	-	>0.2	-
Syncope	0.3	-	-	-	1	-	<2.0	-	✔	<1
Tachycardia	-	≥0.5	1	-	-	-	-	<2	>0.2	-
Central Nervous System										
Anxiety	-	≥0.5	≥1	-	-	-	-	-	>0.2	>0.2
Asthenia	-	≥0.5	-	≥1	-	-	-	-	>0.2	✔
Depression	-	≥0.5	-	-	-	-	-	-	✔	-

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	Valsartan and Nebivolol
Dizziness	8.9	2.9	1 to 8	5.7	-	9	3.0	1 to 7	>0.2 to 6.0	>1 to 4
Fatigue	-	-	-	-	-	-	-	-	-	2
Hallucinations	-	-	-	-	-	-	-	-	-	2 to 5
Headache	-	2.9	1.0 to 5.5	≥1	6.4	>2	-	≥2	-	>1
Hypesthesia	-	≥0.5	-	-	-	-	-	-	-	-
Insomnia	-	≥0.5	-	-	-	-	-	-	>0.2	>0.2 to 9
Nervousness	-	-	≥1	-	-	-	-	-	-	-
Paresthesia	-	≥0.5	-	-	-	-	-	-	>0.2	-
Somnolence	-	-	-	-	-	-	-	-	>0.2	-
Vertigo	-	≥0.5	-	-	-	>1	-	-	>0.2	<1
Dermatological										
Alopecia	-	-	-	-	-	✔	-	-	✔	-
Dermatitis	-	≥0.5	-	-	-	-	-	-	-	✔
Eczema	-	≥0.5	-	-	-	-	-	-	-	-
Pruritus	-	≥0.5	-	-	-	✔	-	-	✔	<1
Rash	-	≥0.5	≥1	1.4	-	>1	-	<2	>0.2	>0.2
Sweating	-	≥0.5	-	-	-	-	-	-	>0.2	-
Urticaria	-	-	✔	-	-	✔	-	-	-	<1
Gastrointestinal										
Abdominal pain	-	≥0.5	2	1.2	-	>1	-	<2	>0.2	2 to 10
Constipation	-	-	-	-	-	-	-	-	✔	-
Diarrhea	-	≥0.5	≥1	≥1	2.6	>1	-	3	>0.2	>1 to 3
Dry mouth	-	-	-	-	-	-	-	-	>0.2	-
Dyspepsia	-	≥0.5	2	-	-	>1	-	<2	>0.2	>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	>1
Vomiting	-	≥0.5	3	-	-	✔	-	<2	>0.2	>1
Laboratory Test Abnormalities										
Bilirubin increased	-	✔	-	✔	-	-	-	✔	-	-
Blood urea nitrogen increased	-	≥0.5	-	0.6	-	1.3	-	2.8	>0.2	1 to 10
Creatine phosphokinase increased	-	≥0.5	-	-	-	>1	-	-	-	-
Hematocrit decreased	-	✔	-	✔	-	0.4	-	0.6	-	-
Hemoglobin decreased	-	✔	-	✔	-	-	-	1.2	-	-
Hypercholesterolemia	-	-	-	-	-	-	-	-	-	1 to 10
Hyperglycemia	-	≥0.5	-	-	-	>1	-	-	-	-
Hyperkalemia	-	-	0.2 to 1.2	-	-	✔	-	-	✔	✔
Hyperlipidemia	-	-	-	-	-	>1	-	-	-	-
Hyperuricemia	-	≥0.5	-	-	-	4	-	-	-	1 to 10
Hypokalemia	-	≥0.5	0.6 to 0.9	-	-	-	-	<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	Valsartan and Nebivolol
Serum creatinine increased	-	✔	-	0.8	-	-	-	1.4	-	-
Thrombocytopenia	-	-	-	✔	-	-	-	-	-	1 to 10
Transaminase levels increased	-	≥0.5	-	✔	-	>1	-	✔	✔	<1
Musculoskeletal										
Arthralgia	-	≥0.5	-	-	-	>1	-	-	>0.2	>1
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	>0.2
Muscle spasms	-	-	-	-	3.1	-	-	-	-	-
Muscle weakness	-	-	-	-	-	-	-	-	✔	1 to 10
Musculoskeletal pain	-	-	6	-	-	-	-	-	-	-
Myalgia	-	≥0.5	-	-	-	>1	-	-	>0.2	>0.2
Pain in extremity	-	-	-	-	-	-	-	-	>0.2	>0.2
Paresthesia	-	-	-	-	-	-	-	-	-	1 to 10
Rhabdomyolysis	-	-	✔	-	-	✔	-	-	✔	-
Sciatica	-	≥0.5	-	-	-	-	-	-	-	-
Respiratory										
Bronchitis	-	≥0.5	-	≥1	-	-	-	<2	>0.2	-
Bronchospasm	-	-	-	-	-	-	-	-	✔	<1
Cough	-	≥0.5	≥1	2.6	-	>1	-	≥2	>0.2	>1
Dyspnea	-	≥0.5	-	-	-	-	-	-	>0.2	≤1
Epistaxis	-	≥0.5	-	-	-	-	-	-	✔	-
Nasal congestion	-	-	-	-	-	-	-	-	>0.2	-
Nasopharyngitis	-	-	-	-	3.5	-	-	2.4	-	-
Pharyngitis	-	≥0.5	≥1	≥1	-	-	-	<2	✔	>1
Pharyngolaryngeal pain	-	-	-	-	-	-	-	-	>0.2	-
Pulmonary edema	-	-	-	-	-	-	-	-	-	<1
Rhinitis	-	≥0.5	≥1	-	-	-	-	-	-	>1
Sinus abnormality	-	-	≥1	-	-	-	-	-	-	-
Sinus congestion	-	-	-	-	-	-	-	-	>0.2	-
Sinusitis	-	≥0.5	-	1.2	-	-	-	4	>0.2	>1
Upper respiratory tract infection	-	3.6	≥1	6.1	2.8	7	-	8	>0.2	>1
Miscellaneous										
Abnormal vision	-	-	-	-	-	-	-	-	✔	-
Acute renal failure	-	-	-	-	-	✔	-	-	-	-
Allergy	-	-	1	-	-	-	-	-	-	✔
Anaphylaxis	-	-	-	-	-	-	-	-	✔	-
Angioedema	-	<0.5	✔	✔	-	✔	-	-	✔	✔
Appetite increased	-	-	-	-	-	-	-	-	✔	-
Conjunctivitis	-	≥0.5	-	-	-	-	-	-	-	-

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	Valsartan and Nebivolol
Cystitis	-	≥0.5	-	-	-	-	-	-	-	-
Dehydration	-	-	-	-	-	-	-	-	✔	-
Dysuria	-	-	-	-	-	-	-	-	✔	-
Edema	-	-	3	1.3	-	-	<2.0	-	-	>1
Erectile dysfunction	-	-	-	-	-	-	-	-	>0.2	-
Facial edema	-	-	-	-	-	✔	-	-	-	-
Fatigue	2.0	≥0.5	6	≥1	4.2		-	3	>0.2	-
Fever	-	-	-	-	-	-	-	-	>0.2	-
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	-	-	-	-	-	-	-	-	✔	<1
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	-	-	-	-	-	-	✔	3

✔ Percent not specified
- Event not reported
HCTZ=hydrochlorothiazide

Table 9. Boxed Warning for the Angiotensin II Receptor Antagonists[21,22]

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[3-22]

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, 0.02 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
Eprosartan	Hypertension: Tablet: initial, 600 mg once daily when used as monotherapy in patients who are not volume-depleted; maintenance, 400 to 800 mg/day in a single or divided dose(s)	Safety and efficacy in children have not been established.	Tablet: 600 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	Cardiovascular risk reduction (hypertension and left ventricular hypertrophy): Tablet: initial, 50 mg once daily;	Hypertension in children ≥6 years of age: Tablet: initial, 0.7 mg/kg once daily (up to 50 mg total);	Tablet: 25 mg 50 mg 100 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	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: 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)	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.	
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 6 to 16 years of age: Tablet: initial, 1.3 mg/kg once daily (up to 40 mg total) administered as a tablet or suspension; maximum, >2.7 mg/kg/day (or in excess of 160 mg) have not been studied Safety and efficacy in children with hypertension <6 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	Safety and efficacy in children have not been established.	Tablet: 40-12.5 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	daily; maintenance, 40-25 mg once daily; maximum, 40-25 mg /day		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
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	Cardiovascular 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
Valsartan and nebivolol	Hypertension: Tablet: 80-5 mg once daily	Safety and efficacy in children have not been established.	Tablet: 80-5 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.[42] (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.[43] (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.[44] (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.[45] (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.[46] (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.[47] (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.[48] (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.[49] (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.[50] (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.[51] (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.[52]	DB, PC, RCT	N=1,513	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2001) 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	Composite of risk of 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	Compared to placebo, losartan resulted in a 16% reduction of composite 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.[53] (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.[54] (2007) ROAD Benazepril 10	OL, PRO, RCT Patients aged 18 to 70 years with proteinuria and	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
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.	chronic renal 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.[55] (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),	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			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	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).
Nakao et al.[56] (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.[57] (2009) TRANSCEND Telmisartan 80 mg QD	DB, MC, PC, RCT Adults with known cardiovascular disease or diabetes with end-organ damage but without	N=5927 56 months	Primary: Composite outcome: first occurrence of dialysis, renal transplant, doubling of serum creatinine,	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	macroalbuminuria or heart failure who cannot tolerate ACE inhibitors		or death Secondary: Changes in the eGFR, progression of proteinuria, and individual components of the primary outcome	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). 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.[58] (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.[59] (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.
Galle et al.[60] (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.[61] (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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 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.[62] (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.[63] (2005)	MA (127 trials)	N=not reported	Primary: Doubling of serum	Primary: Treatment with ACE inhibitors or ARBs resulted in a nonsignificant reduction

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	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.
Strippoli et al.[64] (2004) ACE inhibitors vs placebo or ARBs vs	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo or ACE inhibitors vs ARBs				(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.[65] (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%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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
Heart Failure				
Cohn et al.[66] (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.[67] (2003) CHARM Overall Programme	DB, PC, PG, RCT Summary of all CHARM sub-	N=7,599 37.7 months	Primary: All-cause mortality (Overall Programme) and	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Candesartan 32 mg/day (±ACE inhibitor) vs placebo (±ACE inhibitor)	studies		cardiovascular death or hospital admission for CHF (all of the component trials) Secondary: Not reported	to 0.99; P=0.032). 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.[68] (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.[69] (2003) CHARM-Alternative Candesartan 32 mg/day vs	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	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo			and MI, nonfatal stroke and coronary revascularization	placebo (29%) groups. 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.[70] (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.[71] (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.[72] (1997) ELITE	DB, MC, PG, RCT Patients ≥65 years	N=722 1 year	Primary: Change in renal function	Primary: No difference between losartan and captopril was reported in the rate of persistent rise in serum creatinine concentrations (10.5% for both groups).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Captopril 50 mg TID vs losartan 50 mg QD	with symptomatic heart failure (NYHA class II to IV and LVEF ≤40%), and no history of prior ACE inhibitor therapy		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	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.[73] (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.[74] (1999) RESOLVD Enalapril 10 mg BID	DB, MC, PG, RCT Patients with CHF (NYHA classes II to IV), a 6 minute walk distance of 500	N=768 43 weeks	Primary: Change in 6-minute walk distance Secondary: Change in NYHA	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs candesartan 4 to 16 mg QD vs candesartan 4 to 8 mg QD and enalapril 10 mg BID	meters or less, and an ejection fraction <40%		functional class, QOL, ejection fraction, ventricular volumes, neurohormone levels, safety	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.
Lee et al.[75] (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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Hypertension				
Rakugi et al.[76] (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.[77] (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.[78] (2012) Azilsartan and chlorthalidone 40-25 or 80-25 mg QD (fixed-dose combination product) vs	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,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
olmesartan and HCTZ 40-25 mg QD (fixed-dose combination product)				azilsartan and chlorthalidone 80-25 mg/day, and olmesartan and HCTZ.
Bönner et al.[79] (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.[80] (2016) All subjects initiated treatment with azilsartan 40 mg QD on day one, which was	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
added to existing treatments (a maximum of two 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				frequent with add-on chlorthalidone. Secondary: 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.[81] (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	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
22, chlorthalidone 25 mg QD could be added to 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				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 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%).
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	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
blocking agents				
Baguet et al.[83] (2006) Candesartan 8 mg QD vs losartan 50 mg QD vs placebo	DB, RCT Patients with mild-to-moderate essential HTN (DBP 95 to 115 mm Hg)	N=256 6 weeks	Primary: Change in mean 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	Primary: At the end of the six weeks, the mean change in DBP between the baseline and 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Mengden et al.[85] (2011) CHILI CU Soon Candesartan and HCTZ 32-12.5 or 32-25 mg QD (fixed-dose combination)	MC, OL, PRO High risk patients ≥18 years of age with uncontrolled HTN, on prior antihypertensive agents, and presence of additional cardiovascular risk factors	N=4,131 10 weeks	Primary: Change in baseline office blood pressure and ambulatory blood pressure, safety Secondary: Not reported	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). 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/	MC, OL, PRO, RCT Patients, 20 to 80 years old, with	N=206 8 weeks	Primary: Difference in home morning SBP reduction	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
HCTZ 6.25 mg single pill combination QD vs candesartan 12 mg	newly diagnosed, untreated hypertensive patients or those who were on monotherapy with any antihypertensive drug alone		Secondary: Time-dependent changes in the antihypertensive effects and nocturnal BP reduction	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 (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	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			responders (reduction in DBP ≥5 mm Hg)	Changes in blood chemistry and other secondary measurements were not significantly different between the treatment groups.
Robles et al.[89] (2008) ESTEPP Eprosartan 600 mg QD	MC, OL, PRO Patients with mild-to-moderate HTN with and without diabetes, mean age 65 years for patients with diabetes and 63 years for patients without diabetes	N=549 16 weeks	Primary: Changes in blood pressure, compliance, adverse effects Secondary: Not reported	Primary: Blood pressure decreased significantly (P<0.0001) in both diabetic and nondiabetic patients (SBP 25.9 vs 26.0 mm Hg), DBP (12.5 vs 13.2 mm Hg), MAP (16.9 vs 17.5 mm Hg) and pulse pressure (13.4 vs 12.8 mm Hg). Pulse pressure/MAP ratio showed a significant reduction in diabetics and nondiabetics. Treatment compliance did not differ between the groups (diabetics 98.0% vs nondiabetics 92.2%). The adverse effect rate was 7% in diabetic patients and 2.8% in nondiabetics. Secondary: Not reported
Ruilope et al.[90] (2001) Eprosartan 600 mg QD (titration to 800 mg QD was allowed after 3 weeks) vs enalapril 5 mg QD (titration to 10 mg followed by 20 mg was allowed every 3 weeks	DB, MC, PG, RCT Patients greater than 65 years of age with essential HTN, either newly diagnosed or for whom a change in existing antihypertensive medication is indicated due to poor control	N=334 12 weeks	Primary: Mean change from baseline in sitting SBP Secondary: Normalization rate for sitting SBP and DBP, response rate for sitting SBP and DBP, mean change from baseline in DBP	Primary: No significant difference between groups in change from baseline in sitting SBP was observed (P=0.76). 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 3 (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).
Sachse et al.[91] (2002) Eprosartan 600 mg	DB, MC, PG, PRO, RCT Patients 18 years of	N=309 8 weeks	Primary: Trough sitting DBP Secondary:	Primary: Significantly greater reductions in sitting DBP were observed at study endpoint in the eprosartan and HCTZ group compared to the eprosartan monotherapy group (P=0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD vs eprosartan 600 mg and HCTZ 12.5 mg QD	age and older with mild- to moderate HTN		Trough sitting SBP and HR, proportion of patients whose sitting DBP had normalized, proportion of responders (defined as normal sitting DBP or sitting DBP ≤100 mm Hg and decreased from baseline by at least 10 mm Hg)	Secondary: Significantly greater reductions in sitting SBP were observed at study endpoint in the eprosartan and HCTZ group compared to the eprosartan monotherapy group (P=0.001). No significant difference was observed between groups in the proportion of patients whose sitting DBP had normalized (P=0.10). The response rate was significantly higher in the eprosartan and HCTZ group compared to the eprosartan monotherapy group (P=0.004).
Ambrosioni et al.[92] 2010 INSIST Eprosartan and HCTZ 600-12.5 mg QD (fixed-dose combination product) vs losartan and HCTZ 50-12.5 mg QD (fixed-dose combination product)	DB, DD, MC, PG, PC, RCT Patients 60 years of age and older meeting the WHO criteria for grade 2 systolic HTN	N=155 6 weeks	Primary: Mean change from end of wash-out period to the end of combination therapy in ABPM SBP Secondary: Pulse pressure, SBP at daytime, SBP at nighttime, SBP in the last 4 hours before taking study medication, hourly SBP, response rate	Primary: No significant difference was observed between the eprosartan and losartan groups in mean change in ABPM SBP (P≥0.075). Secondary: No significant differences were observed between groups in any secondary endpoints.
Gradman et al.[93] (2005) Irbesartan 150 mg QD	DB, MC, PC, PG, RCT Men and women, age 18 years or older, with mild-to-	N=652 8 weeks	Primary: Change in mean sitting DBP and SBP Secondary:	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs aliskiren 150 to 600 mg QD vs placebo	moderate essential HTN (mean sitting DBP ≥95 mm Hg and <110 mm Hg)		Proportion of patients achieving blood pressure control (<140/90 mm Hg), safety	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.[94] (2007) Irbesartan 150 to 300 mg QD, added to existing HCTZ therapy (single entity products) vs aliskiren 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	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

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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)			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 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.[95] (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 aliskiren 150 mg QD for 3 weeks, then HCTZ 25 mg QD was added for an additional 3 weeks (if ABPM	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

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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				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.[96] (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.[97] (2006) Irbesartan 150 to 300 mg QD vs	AC, DB, MC, RCT Patients ≥18 years with severe HTN who were untreated (seated DBP ≥110 mm Hg) or currently receiving	N=737 7 weeks	Primary: Proportion of patients with DBP <90 mm Hg at week 5 Secondary: Proportion of	Primary: Significantly more patients on combination therapy achieved seated DBP <90 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

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irbesartan and HCTZ 150 to 300-12.5 to 25 mg QD (fixed-dose combination)	antihypertensive monotherapy with DBP ≥100 mm Hg		patients who achieved seated SBP/DBP <140/90 mm Hg	Hg, respectively (P<0.0001). Greater and more rapid blood pressure reduction with irbesartan and HCTZ was achieved without additional side effects.
Neutel (abstract).[98] (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.[99] (2008) Irbesartan and HCTZ 300-25 mg QD (fixed-dose combination product) vs irbesartan 300 mg QD	AC, DB, RCT 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)	N=538 12 weeks	Primary: Change in SBP 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	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 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%;

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vs HCTZ 25 mg QD			weeks 8 and 12	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.[100] (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.[101] (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.
Stanton et al.[102] (2003) Losartan 100 mg QD	AC, DB, MC, RCT Men and women 21 to 70 years of age with mild-to-moderate HTN	N=226 4 weeks	Primary: Change in daytime ambulatory SBP Secondary: Changes in clinic	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

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vs aliskiren 37.5 to 300 mg QD	(SBP ≥140 mm Hg)		SBP and DBP, plasma renin activity, plasma aliskiren levels, adverse events	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.[103] (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 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

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Oparil et al.[104] (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.[105] (2002) LIFE 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	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).

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pressure control.				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.[106] (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.[107] (2002) LIFE Diabetic Subset Losartan 50 to 100 mg QD vs atenolol 50 to 100 mg QD	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.

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HCTZ 12.5 to 25 mg QD was added if needed for blood pressure control.				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.[108] (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.[109] (2006) ICARUS, a LIFE substudy Losartan 50 to 100 mg/day vs atenolol 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 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

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All patients received HCTZ 12.5 to 25 mg/day if need for blood pressure control.				
Kizer et al.[110] (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.[111] (2005) LIFE substudy Losartan 50 to 100 mg/day vs atenolol 50 to 100 mg/day All patients	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 atrial fibrillation but at risk for atrial fibrillation) ≥4 years	Primary: Incidence of new-onset atrial fibrillation and outcome Secondary: Not reported	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). 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

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received HCTZ 12.5 to 25 mg/day if need for blood pressure control.				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.[112] (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
Van Bortel et al.[113] (2005) Losartan 50 mg QD	DB, MC, PG, RCT Patients <70 years of age with DBP at randomization between 95 and 114	N=314 12 weeks	Primary: Effects on blood pressure, overall QOL Secondary:	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

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vs nebivolol 5 mg QD If after 6 weeks, DBP was not normalized, then HCTZ 12.5 mg QD was added to therapy	mm Hg		Comparison of different aspects of QOL	(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.[114] (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 eplerenone in patients with various baseline renin and aldosterone levels,	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 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

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			adverse effects	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.[115] (2007) SALT Losartan 100 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	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 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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 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).
Maeda et al.[116] (2012) ARCH	MC, OL, OS, PRO Patients 20 to 80 years of age with	N=614 52 weeks	Primary: Change in blood pressure at 3 months	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Losartan and HCTZ (fixed-dose combination product)	HTN uncontrolled by either ARB monotherapy or combination with and ARB and a calcium channel blocker		Secondary: Not reported	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.[117] (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.[118] (2004) Losartan and HCTZ 50-12.5 to 100-25 mg QD (fixed-dose combination product)	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%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs losartan 50 to 100 mg QD Doses were titrated as needed to reach blood pressure goal (<90 mm Hg).				
Minami et al.[119] (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.[120] (2003) PROBE Losartan and HCTZ 50-12.5 mg QD (fixed-dose combination	DB, MC, OL, RCT Patients ≥18 years of age with mild-to-moderate essential HTN	N=597 6 weeks	Primary: Mean changes in ambulatory DBP Secondary: Mean changes in ambulatory SBP, 24-hour DBP, safety	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 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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)				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.[121] (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: Not reported	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: Not reported
Punzi et al.[122] (2012)	DB, PRO, RCT Patients with HTN	N=941 8 weeks	Primary: Change in baseline seated cuff DBP at	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;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Olmesartan 20 mg QD, up titrated to 40 mg QD vs losartan 50 mg QD, up titrated to 100 mg QD	no previously treated or previously treated with antihypertensive medications		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	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.[123] (2001) Olmesartan 20 mg QD vs irbesartan 150 mg QD, losartan 50 mg QD, or valsartan 80 mg QD	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 ≥90 mm Hg and <120 mm Hg)	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. Secondary: Reductions of cuff SBP were not significantly different among the four ARBs and ranged from 8.4 to 11.3 mm Hg.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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.[124] (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 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 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. All treatments were well tolerated.
Kereiakes et al.[125] (2007)	DB, DD, MC, PG, RCT	N=190 12 weeks	Primary: Change in mean seated SBP at the	Primary: Patients treated with olmesartan and HCTZ experienced significantly greater reductions in mean seated SBP at week 12 than patients treated with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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	Patients with stage 2 HTN		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	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.[126] (2008) COACH Olmesartan 10 to 40 mg QD vs	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	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
amlodipine 5 to 10 mg QD vs olmesartan 10 to 40 mg and amlodipine 5 to 10 mg QD vs placebo			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	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.[127] (2009) COACH Olmesartan 10 to 40 mg QD and amlodipine 5 to 10 mg QD HCTZ 12.5 to 25 mg could be added if blood pressure was not controlled (<140/90 mm Hg	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 <130/80 mm Hg for patients with diabetes)	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 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
or <130/80 mm Hg in patients with diabetes).				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.[128] (2009) 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	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) and no prior antihypertensive medication	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 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				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.[129] (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.[130] (2012) TRINITY Olmesartan and amlodipine and HCTZ 40-10-25 mg/day (fixed-dose combination product) vs component dual-combination treatments	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 treatment achieved blood pressure goal compared to combination therapies, regardless of race. No new safety concerns were identified with any treatment. The majority of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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.[131] (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.[132] (2011) TRINITY Olmesartan and amlodipine and HCTZ 40-10-25 mg/day (fixed-dose combination product) vs component dual-combination treatments	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. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Punzi, HA[133] (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.[134] (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.[135] (2009) PRISMA I and PRISMA II	Pooled analysis: blinded endpoint, OL, PRO, RCT Patients ≥18 years	N=1,613 14 weeks	Primary: Change from baseline in mean ambulatory BP during the final 6	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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	of age with mild- to moderate HTN		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	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.[136] (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).
Xi et al.[137]	MA	N=1,832	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2008) Telmisartan vs losartan	Patients with HTN	(11 trials) Variable duration	Reduction in DBP and SBP Secondary: Therapeutic response of DBP and SBP, tolerability	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.[138] (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 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(5.7%), dizziness and cough (3.8%), and diarrhea (1.9%). Secondary: Not reported
Littlejohn et al.[139] (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.[140] (2009) Telmisartan and amlodipine 40-5	DB, DD, MC, PC, PG, RCT Patients ≥18 years of age with stage 1	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). Amlodipine 5 and 10 mg with telmisartan 40 and 80 mg significantly reduced

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 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	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	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.[141] (2012)	DB, MC, PG, RCT	N=858	Primary: Change in baseline	Primary: Reductions in seated trough cuff blood pressure (-47.5/-18.7 mm Hg) were

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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	blood pressure, blood pressure goal and response rates Secondary: Safety	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.[142] (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 mm Hg), change in	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 alone

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo			24-hr ABPM, change in biomarkers, safety	(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.[143] (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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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. 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.
Pool et al.[144] (2007) Aliskiren 75 to 300 mg QD vs	DB, MC, PC, PG, RCT Men and women ≥18 years with mild-to-moderate essential HTN (mean sitting DBP	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: Aliskiren 300 mg significantly (P<0.0001) lowered mean sitting SBP

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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	≥95 mm Hg after a 3- to 4-week single-blind placebo run-in period)			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.[145] (2009) Aliskiren 150 to 300 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	N=641 8 weeks	Primary: Change in DBP at week 8 Secondary: Change SBP at week 8, change in	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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	weeks with a DBP ≥95 mm Hg		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	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.[146] (2006) Valsartan 80 to 160 mg QD vs amlodipine 5 to 10 mg QD	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 treatment, percent	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
If blood pressure exceeded 140/90 while on highest treatment dose, HCTZ 12.5mg/day was added to the regimen.			of patients who achieved goal <140/<90 with each treatment based on clinic blood pressure measurements	
Ichihara et al.[147] (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).
Philipp et al.[148] (2007) <u>Study 1</u> Valsartan 40 to 320 mg QD and amlodipine 2.5 to 5 mg QD	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	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs amlodipine 2.5 to 5 mg QD vs valsartan 40 to 320 mg QD vs placebo			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)	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). 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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.[149] (2007) Study 2 Valsartan 160 or 320 mg QD and amlodipine 10 mg QD vs amlodipine 10 mg QD vs valsartan 160 to 320 mg QD vs placebo	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 patients with mean sitting DBP <90 mm Hg), adverse events (combined with study 1)	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).
Sinkiewicz et al.[150] (2009) Amlodipine and valsartan 10-160 mg or 5-160 mg QD (fixed-dose combination product) vs valsartan 160 mg	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	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD			baseline), and DBP control rate (mean DBP < 90 mm Hg)	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).[151] (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	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				
Fogari et al.[151] (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) were significant for those receiving irbesartan and HCTZ, but not valsartan and amlodipine (P<0.05 for irbesartan and HCTZ).
Poldermans et al.[152] (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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The response rate was similar among the groups (100 vs 95.5%; P value not significant).
White et al.[153] (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.[154] (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
Schweizer et al.[155] (2007) Valsartan and	OL Hypertensive patients not	N=197 8 weeks	Primary: Reduction in mean sitting DBP between week 4 and 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
HCTZ 160-25 mg QD (fixed-dose combination)	adequately controlled by free combination of candesartan and HCTZ for 4 weeks		Secondary: Reduction in mean sitting SBP from week 4 to 8	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.[156] (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: Not reported
Izzo Jr et al.[157] (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	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
All patients were allowed to up titrate study medication if blood pressure did not improve.				
Duprez et al.[158] (abstract) (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.	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). Secondary: In the overall study, tolerability was similar among the three treatment groups.
Fogari et al.[159] (2006)	PG, PRO, RCT Hypertensive	N=130 8 weeks	Primary: Changes in blood pressure	Primary: Both combinations induced a greater ambulatory blood pressure reduction than monotherapy. However, mean reduction from baseline in the valsartan and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Valsartan 160 mg vs olmesartan 20 mg All patients were also receiving HCTZ 12.5 mg QD.	patients aged 35 to 75 years with DBP 90 to 110 mm Hg after 4 weeks of monotherapy on either valsartan or olmesartan	(4 weeks of combination therapy)	Secondary: Not reported	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.[160] (2008) Valsartan 160 mg and HCTZ 25 mg QD vs telmisartan 80 mg and HCTZ 25 mg QD 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 3 treatment groups and was 37% for valsartan and HCTZ, 36% for telmisartan and HCTZ, and 42% for placebo.
Sharma et al.[161] (2007) SMOOTH Valsartan 160 mg for 4 weeks vs	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	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;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
telmisartan 80 mg for 4 weeks After 4 weeks, all patients received add-on HCTZ 12.5 mg QD for 6 six weeks.	Hg and/or DBP 95 to 109 mm Hg), with type 2 diabetes and BMI >27 kg/m^2			P=0.0006) and during morning, daytime and nighttime periods (P<0.003). Both treatments were well tolerated. 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 mg QD (fixed-dose combination product) vs amlodipine and HCTZ 10-25 mg QD (fixed-dose combination product) vs amlodipine and valsartan and	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). Triple therapy with amlodipine and valsartan and HCTZ improved blood pressure control significantly better than any of the dual therapies. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
HCTZ 10-320-25 mg QD (fixed-dose combination product)				
Calhoun et al.[163] (2009) 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) vs amlodipine and valsartan and HCTZ 10-320-25 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Karotsis et al.[164] (2006) Valsartan 80 mg QD vs lisinopril 10 mg QD vs chlorthalidone 12.5 mg QD vs felodipine 5 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
Conlin et al.[165] (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	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%.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs another ARB vs ARB plus low-dose HCTZ				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.[166] (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
Lindholm et al.[167] (2005) Other antihypertensive therapies (amiloride, amlodipine, bendro-flumethiazide*, captopril, diltiazem, enalapril, felodipine, HCTZ, isradipine,	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
lacidipine, lisinopril, losartan, or verapamil) or placebo vs β-blocker therapy (atenolol, metoprolol, oxprenolol*, pindolol, or propranolol)				
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). 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,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 dosages. Although cicletanine*, furosemide and spironolactone	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
were considered for inclusion, none of the trials relating to these agents satisfied all inclusion criteria.				
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 amlodipine 2.5 to 10 mg QD	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 mm Hg or DBP ≥90 mm Hg in patients ≥70 years old), with either type 2 diabetes, history of stroke or ischemic	N=4,703 Up to 4 years	Primary: First fatal or nonfatal cardiovascular event Secondary: All-cause death, new-onset diabetes, discontinuation due to adverse events	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. 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	attack, left ventricular hypertrophy, proteinuria or serum creatinine ≥1.3 mg/dL			
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 20 mg QD on day 15 vs	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 Secondary: Changes in other inflammatory markers such as troponin I	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: 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
irbesartan 150 mg QD, followed by 300 mg QD on day 15				
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 All patients received pravastatin 20 mg/day after six weeks of therapy.	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 tumor necrosis factor-α, interleukin-6 Secondary:	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. 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:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Not reported	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 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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). 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)	Subgroup analysis of VALUE	N=15,245	Primary: Time to first cardiac	Primary: The only significant result of the analyses by subgroup for time to first cardiac

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	event, analyzed by subgroup Secondary: MI, heart failure and stroke	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 or <130/80 mm Hg vs antihypertensive	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 dialysis) Secondary: Not reported	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: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
agents (other than ACE inhibitors and ARBs) to reach target blood pressure <140/90 or <130/80 mm Hg				
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 Secondary: Not reported	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
Blood Pressure Lowering	MA	N=146,838 (26 trials)	Primary: Nonfatal MI or	Primary: From a total of 146,838 individuals with high blood pressure or an elevated

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Treatment Trialists' Collaboration[185] (2007) ACE inhibitors (17 trials) vs ARBs (9 trials)	Patients with high blood pressure, diabetes, history or CHD or cerebrovascular disease	Variable duration	death from CHD, including sudden death; heart failure causing death or requiring hospitalization; nonfatal stroke or death from cerebrovascular disease Secondary: Not reported	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
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 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®	$$$	N/A
Candesartan	tablet	Atacand®*	$$$$	$$$
Eprosartan	tablet	N/A	N/A	$$$
Irbesartan	tablet	Avapro®*	$$$	$
Losartan	tablet	Cozaar®*	$$$$	$
Olmesartan	tablet	Benicar®*	$$$	$
Telmisartan	tablet	Micardis®*	$$$$	$$
Valsartan	tablet	Diovan®*	$$$$	$
Combination Products				
Azilsartan and chlorthalidone	Tablet	Edarbyclor®	$$$$	N/A
Candesartan and HCTZ	tablet	Atacand HCT®*	$$$$	$$$$
Irbesartan and HCTZ	tablet	Avalide®*	$$$$	$
Losartan and HCTZ	tablet	Hyzaar®*	$$$$	$
Olmesartan and amlodipine and hydrochlorothiazide	tablet	Tribenzor®*	$$$$$	$$$$
Olmesartan and HCTZ	tablet	Benicar HCT®*	$$$$$	$
Telmisartan and amlodipine	tablet	Twynsta®*	$$$$	$$$

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Telmisartan and HCTZ	tablet	Micardis HCT®*	$$$$	$$$$
Valsartan and HCTZ	tablet	Diovan HCT®*	$$$$	$
Valsartan and nebivolol	tablet	Byvalson®	$$$$	N/A

*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).[3-20] 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, olmesartan is available in combination with amlodipine and hydrochlorothiazide (triple therapy), and valsartan is available in combination with nebivolol. 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 and valsartan-nebivolol.

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.[23-41] In general, guidelines do not give preference to one ARB over another.[23-41] 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.[23,25-33,38] Thiazide-type diuretics are frequently recommended as initial therapy in patients with uncomplicated hypertension.[34-39] 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).[34] Several guidelines consistently recommend that the selection of an antihypertensive agent be based on compelling indications for use.[34-40] Most patients will require more than one antihypertensive medication to achieve blood pressure goals.[34-39]

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.[76-170] 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.[34-39] The use of a fixed-dose combination product may simplify the treatment regimen and improve adherence.[36-37,40] 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.[42-65] 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.[42,43,45,47,52-56,59,65,67,72-75,178] 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.[21,22]

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.[186] 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.[187]

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
November 8, 2017

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 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.[1-5] 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]

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 products are available in a generic formulation. This class was last reviewed in August 2015.

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
Spironolactone	tablet	Aldactone®*	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 College of Cardiology/American Heart Association: **2007 Chronic Angina Focused Update of the 2002 Guidelines for the Management of Patients With Chronic Stable Angina**	• Aspirin should be started at 75 to 162 mg/day and continued indefinitely in all patients, unless contraindicated. • Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with an increased risk of bleeding and should be monitored closely. • Patients with hypertension and established coronary artery disease (CAD) should be treated with blood pressure medication(s) as tolerated, including angiotensin-converting enzyme inhibitors (ACE inhibitors) and/or β-adrenergic antagonists (β-blockers) with the addition of other medications as needed to achieve blood pressure goals of <140/90 or <130/80 mm Hg for patients with chronic kidney disease or diabetes.

Clinical Guideline	Recommendations
(2007)[6]	• Long-acting calcium-channel blocking agents or long-acting nitrates may be used if β-blockers are contraindicated. Immediate-release and short-acting dihydropyridine calcium channel blockers can increase adverse cardiac events and should not be used. • Long-acting calcium channel blockers or long-acting nitrates may be used with β-blockers if initial treatment is not successful. • ACE inhibitors should be used indefinitely in patients with a left ventricular ejection fraction (LVEF) of ≤40% and in those with hypertension, diabetes or chronic kidney disease, unless contraindicated. • ACE inhibitors should also be used indefinitely in patients at lower risk (mildly reduced or normal LVEF in whom cardiovascular risk factors remain well controlled and revascularization has been performed), unless contraindicated. • Angiotensin II receptor blockers (ARBs) are recommended in patients with hypertension, those who have an indication for an ACE inhibitor and are intolerant to them, who have heart failure, or who have had a myocardial infarction (MI) and have a LVEF of ≤40%. • ARBs may be considered in combination with an ACE inhibitor for heart failure due to left ventricular systolic dysfunction. • Aldosterone blockade is recommended in patients post-MI without significant renal dysfunction or hyperkalemia who are already receiving therapeutic doses of an ACE inhibitor and a β-blocker, have a LVEF ≤40% and have either diabetes or heart failure. • It is beneficial to start and continue β-blocker therapy indefinitely in all patients who have had a MI, acute coronary syndrome or left ventricular dysfunction with or without heart failure symptoms, unless contraindicated. • Annual influenza vaccination is recommended in patients with cardiovascular disease.
European Society of Cardiology: **Guidelines on the Management of Stable Coronary Artery Disease (2013)[7]**	<u>General management of stable coronary artery disease (SCAD) patients</u> • The goal of management of SCAD is to reduce symptoms and improve prognosis. • The management of CAD patients encompasses lifestyle modification, control of CAD risk factors, evidence-based pharmacological therapy, and patient education. <u>General considerations for pharmacological treatments in SCAD patients</u> • 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. <u>Pharmacological treatments for angina/ischemia relief in SCAD patients</u> • Short-acting nitrates are recommended. • First-line treatment is indicated with ß-blockers and/or calcium channel blockers to control heart rate and symptoms. • For second-line treatment it is recommended to add long-acting nitrates or ivabradine or nicorandil* or ranolazine, according to heart rate, blood pressure, and tolerance. • For second-line treatment, trimetazidine* may be considered. • 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 β-blockers avoided.

Clinical Guideline	Recommendations
	Pharmacological treatments for event prevention in SCAD patients • Low-dose aspirin daily is recommended in all SCAD patients. • Clopidogrel is indicated as an alternative in case of aspirin intolerance. • Statins are recommended in all SCAD patients. • It is recommended to use ACE inhibitors (or ARBs) if presence of other conditions (e.g. heart failure, hypertension or diabetes). Treatment in patients with microvascular angina • It is recommended that all patients receive secondary prevention medications including aspirin and statins. • β-blockers are recommended as a first line treatment. • Calcium antagonists are recommended if β-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 (aminophylline, bamiphylline*) or non-pharmacological treatments such as neurostimulatory techniques may be considered in patients with symptoms refractory to the above listed drugs.
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)[8]**	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	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%,

Clinical Guideline	Recommendations
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)[9]**	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 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

Clinical Guideline	Recommendations
	▪ 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 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, $P2Y_{12}$

Clinical Guideline	Recommendations

	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 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

Clinical Guideline	Recommendations
	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 patients treated with ticagrelor and 81 to 325 mg daily in all other patients. ○ 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. ○ 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 ○ 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. ○ 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: **Guideline for the Management of Acute Coronary Syndromes in Patients Presenting Without Persistent ST-Segment Elevation (2015)[10]**	Pharmacological treatment of ischemia • Early initiation of β-blocker treatment is recommended in patients with ongoing ischemic symptoms and without contraindications. • 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. Recommendations for platelet inhibition in non-ST-elevation acute coronary syndromes • 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. ○ 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. • 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

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	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 CHADS2-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. • 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 CHADS2-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

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	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.
American College of Cardiology/American Heart Association: **Guideline for the Management of ST-Elevation Myocardial Infarction (2013)**[11]	Routine medical therapies: β-blockers • 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. Routine medical therapies: renin-angiotensin-aldosterone system inhibitors • 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. 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 (2012)**[12]	Routine therapies in the acute, subacute and long term phase of STEMI • Active smokers with STEMI must receive counseling and be referred to a smoking cessation program. • Each hospital participating in the care of STEMI patients must have a smoking cessation protocol. • Exercise-based rehabilitation is recommended. • Antiplatelet therapy with low dose aspirin (75 to 100 mg) is indicated indefinitely after STEMI. • In patients intolerant to aspirin, clopidogrel is indicated as an alternative. • Dual antiplatelet therapy with a combination of aspirin and prasugrel or aspirin and ticagrelor is recommended (over aspirin and clopidogrel) in patients treated with PCI. • Dual antiplatelet therapy with aspirin and an oral ADP receptor antagonist must be continued for up to 12 months after STEMI, with a strict minimum of 1 month for patients receiving bare metal stent and 6 months for patients receiving drug-eluting stent.

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	• In patients with left ventricular thrombus, anticoagulation should be instituted for a minimum of 3 months. • In patients with a clear indication for oral anticoagulation (e.g. atrial fibrillation with CHA2DS2-VASc Score ≥2 or mechanical valve prosthesis), oral anticoagulation must be implemented in addition to antiplatelet therapy. • If patients require triple antithrombotic therapy, combining dual antiplatelet therapy and oral anticoagulant, e.g. because of stent placement and an obligatory indication for oral anticoagulation, the duration of dual antiplatelet therapy should be minimized to reduce bleeding risk. • 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 1 year in patients with STEMI who did not receive a stent. • Gastric protection with a proton pump inhibitor should be considered for the duration of DAPT therapy in patients at high risk of bleeding. • 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. • Intravenous β-blockers must be avoided in patients with hypotension or heart failure. • Intravenous β-blockers should be considered at the time of presentation in patients 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. • Reassessment of LDL-cholesterol should be considered after 4–6 weeks to ensure that a target value of ≤70 mg/dL has been reached. • Verapamil may be considered for secondary prevention in patients with absolute contraindications to β-blockers and no heart failure. • 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.

National Institute for Health and Clinical Excellence: **Myocardial Infarction: cardiac rehabilitation and prevention of further cardiovascular disease (2013)**[13]	Drug therapy
	• Offer all people who have had an acute MI treatment with the following drugs:
	  ○ ACE inhibitor
	  ○ Dual antiplatelet therapy (aspirin plus a second antiplatelet agent)
	  ○ β-blocker
	  ○ Statin
	
	Antiplatelet therapy
	• Offer aspirin to all people after an MI and continue indefinitely, unless they are aspirin intolerant or have an indication for anticoagulation.
	• Offer aspirin to people who have had an MI more than 12 months ago and

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	continue it indefinitely. • For patients with aspirin hypersensitivity, clopidogrel monotherapy should be considered as an alternative treatment. • Special considerations should be made for people with dyspepsia. • After appropriate treatment, people with a history of aspirin-induced ulcer bleeding whose ulcers have healed and who are negative for Helicobacter pylori should be considered for treatment in line with dyspepsia. • Ticagrelor in combination with low-dose aspirin is recommended for up to 12 months as a treatment option in adults with ACS (STEMI, PCI, or NSTEMI). • Offer clopidogrel as a treatment option for up to 12 months to people who have had an NSTEMI, regardless of treatment, or people who have had a STEMI and received a bare-metal or drug-eluting stent. • Offer clopidogrel as a treatment option for at least one month and consider continuing for up to 12 months in people who have had a STEMI and medical management with or without reperfusion treatment with a fibrinolytic agent. • Continue the second antiplatelet agent for up to 12 months in people who have had a STEMI and who received CABG surgery. • Offer clopidogrel instead of aspirin to people who also have other clinical vascular disease (had an MI and stopped dual antiplatelet therapy or had an MI more than 12 months ago). <u>Antiplatelet therapy in people with an indication for anticoagulation</u> • Take bleeding risk, thromboembolic risk, and cardiovascular risk into account when deciding which people who have had an MI and have an indication for anticoagulation. • Unless there is a high risk of bleeding, continue anticoagulation and add aspirin to treatment in people who have had an MI who otherwise need anticoagulation and who have had their condition managed medically or have undergone balloon angioplasty or have undergone CABG surgery. • Continue anticoagulation and add clopidogrel to treatment in people who have had an MI, who have undergone PCI with bare-metal or drug-eluting stents and who otherwise need anticoagulation. • Offer clopidogrel with warfarin to people with a sensitivity to aspirin who otherwise need anticoagulation and aspirin and who have had an MI. • Do not routinely offer warfarin in combination with prasugrel or ticagrelor to people who need anticoagulation who have had an MI. • After 12 months since the MI, continue anticoagulation and take into consideration the need for ongoing antiplatelet therapy, taking into account all of the following: indication for anticoagulation, thromboembolic risk, bleeding risk, cardiovascular risk and the person's wishes. • Do not add a new oral anticoagulant (rivaroxaban, apixaban or dabigatran) in combination with dual antiplatelet therapy in people who otherwise need anticoagulation, who have had an MI. • Consider using warfarin and discontinuing treatment with a new oral anticoagulant (rivaroxaban, apixaban, or dabigatran) in people who otherwise need anticoagulation and who have had an MI, unless there is a specific clinical indication to continue it.
American College of Cardiology/American Heart Association: **Guideline for the Management of Heart Failure (2013)**[14]	<u>Treatment of Stage A heart failure (HF)</u> • Hypertension and lipid disorders should be controlled in accordance with guidelines to lower the risk of HF. (Level of Evidence (LoE): A) • Other conditions that may lead to or contribute to HF, such as obesity, diabetes mellitus, tobacco use, and known cardiotoxic agents, should be controlled or avoided. (LoE: C) <u>Treatment of Stage B heart failure</u>

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	• In patients with a history of MI and reduced EF, ACE inhibitors or ARBs should be used to prevent HF. (LoE: A) • In patients with MI and reduced EF, evidence-based β-blockers (using one of three proven to reduce mortality [i.e., bisoprolol, carvedilol, and sustained-release metoprolol succinate]) should be used to prevent HF. (LoE: B) • In patients with MI, statins should be used to prevent HF. (LoE: A) • ACE inhibitors and β-blockers should be used in all patients with a reduced EF to prevent symptomatic HF, even if they do not have a history of MI. (LoE: A and C, respectively) • Blood pressure should be controlled to prevent symptomatic HF. (LoE: A) • Nondihydropyridine calcium channel blockers may be harmful in patients with low LVEF. (LoE: C) <u>Pharmacological treatment for Stage C HFrEF</u> • Recommendations for patients in Stages A and B are recommended where appropriate for patients in Stage C. (LoE: A, B, and C as appropriate) • Diuretics are recommended in patients with HFrEF who have evidence of fluid retention, unless contraindicated, to improve symptoms. (LoE: C) • ACE inhibitors are recommended in patients with HFrEF and current or prior symptoms, unless contraindicated, to reduce morbidity and mortality. ARBs are recommended as alternative therapy in ACE inhibitor intolerant patients. (LoE: A) • Use of one of the three β-blockers proven to reduce mortality is recommended for all patients with current or prior symptoms of HFrEF, unless contraindicated, to reduce morbidity and mortality. (LoE: A) • Aldosterone receptor antagonists are recommended in patients with NYHA class II–IV HF and who have LVEF of ≤35%, unless contraindicated, to reduce morbidity and mortality. Patients with NYHA class II HF should have a history of prior cardiovascular hospitalization or elevated plasma natriuretic peptide levels to be considered for aldosterone receptor antagonists. Creatinine should be ≤2.5 mg/dL in men or ≤2.0 mg/dL in women (or estimated glomerular filtration rate >30 mL/min/1.73 m^2), and potassium should be <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) • The combination of hydralazine and isosorbide dinitrate is recommended to reduce morbidity and mortality for patients self-described as African Americans with NYHA class III–IV HFrEF receiving optimal therapy with ACE inhibitors and β-blockers, unless contraindicated. (LoE: A) • Digoxin can be beneficial in patients with HFrEF, unless contraindicated, to decrease hospitalizations for HF. (LoE: B) • Patients with chronic HF with permanent/persistent/paroxysmal AF and an additional risk factor for cardioembolic stroke (history of hypertension, diabetes mellitus, previous stroke or transient ischemic attack, or ≥75 years of age) should receive chronic anticoagulant therapy. (LoE: A) • Statins are not beneficial as adjunctive therapy when prescribed solely for the diagnosis of HF in the absence of other indications for their use. (LoE: A) • Calcium channel blockers are not recommended as routine treatment for patients with HFrEF. (LoE: A) <u>Pharmacological treatment for Stage C HFpEF</u> • Blood pressure should be controlled according to published clinical practice guidelines. (LoE: B) • Diuretics should be used for relief of symptoms due to volume overload. (LoE: C)

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	• The use of β-blocking agents, ACE inhibitors, and ARBs in patients with hypertension is reasonable to control blood pressure in patients with HFpEF. (LoE: C) <u>Treatment of Stage D (advanced/refractory) HF</u> • Fluid restriction (1.5 to 2 L/d) is reasonable, especially in patients with hyponatremia, to reduce congestive symptoms. (LoE: C) • Until definitive therapy (e.g., coronary revascularization, mechanical circulatory support, heart transplantation) or resolution of the acute precipitating problem, patients with cardiogenic shock should receive temporary intravenous inotropic support to maintain systemic perfusion and preserve end-organ performance. (LoE: C) • Continuous intravenous inotropic support is reasonable as "bridge therapy" in patients with stage D HF refractory to medical therapy and device therapy who are eligible for and awaiting mechanical circulatory support or cardiac transplantation. (LoE: B) • Long-term use of either continuous or intermittent, intravenous parenteral positive inotropic agents, in the absence of specific indications or for reasons other than palliative care, is potentially harmful in the patient with HF. (LoE: B)
Heart Failure Society of America: **Heart Failure Society of America 2010 Comprehensive Heart Failure Practice Guidelines (Executive Summary) (2010)[15]**	<u>Patients with left ventricular systolic dysfunction</u> • ACE inhibitors should be used in all patients with a LVEF ≤40%, unless otherwise contraindicated. • ARBs may be used in patients who are intolerant to ACE inhibitors. Hydralazine and a nitrate may be used in patients intolerant to ACE inhibitors and ARBs, or in whom such therapy is contraindicated. • The combination of an ACE inhibitor and a β-blocker is recommended in all patients with a LVEF ≤40%. • The routine use of an ARB with a combination of an ACE inhibitor and β-blocker in patients who have had a MI and have left ventricular dysfunction is not recommended. • The addition of an ARB can be considered in patients with heart failure due to reduced LVEF who have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor and a β-blocker. • Individual ARBs may be considered as initial therapy (instead of an ACE inhibitor) in patients with heart failure who have had a MI and in patients with chronic heart failure and systolic dysfunction. • ARBs are recommended in patients who cannot tolerate ACE inhibitors due to cough. The combination of hydralazine and an oral nitrate may be considered in such patients not tolerating ARB therapy. • Patients intolerant to ACE inhibitors from hyperkalemia or renal insufficiency are likely to experience the same side effects with ARBs. In these cases, the combination of hydralazine and an oral nitrate should be considered. • ARBs should be considered in patients experiencing angioedema while on ACE inhibitors based on their underlying risk and with recognition that angioedema has been reported infrequently with ARBs. The combination of hydralazine and oral nitrates may be considered in such patients not tolerating ARB therapy. • A combination of hydralazine and an oral nitrate is recommended in African American patients with heart failure and reduced left ventricular ejection fraction (LVEF) who are on a standard regimen of an ACE inhibitor (or ARB) and a β-blocker. • A combination of hydralazine and an oral nitrate may be considered in non–African American patients with heart failure and reduced LVEF who are symptomatic despite optimization of standard therapy. • Administration of an aldosterone antagonist is recommended for patients with New York Heart Association (NYHA) class IV (or class III, previously class IV)

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	heart failure from reduced LVEF (<35%) while receiving standard therapy, including diuretics. • Administration of an aldosterone antagonist should be considered in patients following an acute MI, with clinical heart failure signs and symptoms or history of diabetes mellitus, and an LVEF <40%. Patients should be on standard therapy, including an ACE inhibitor (or ARB) and a β-blocker. • The triple combination of an ACE inhibitor, an ARB, and an aldosterone antagonist is not recommended because of the high risk of hyperkalemia. <u>Patients with hypertension and symptomatic left ventricular dysfunction with left ventricular dilation and low LVEF</u> • ACE inhibitors, ARBs, β-blockers, aldosterone inhibitors, and isosorbide dinitrate/hydralazine in various combinations (with a loop diuretic if needed) are recommended. • If blood pressure remains >130/80 mm Hg, a dihydropyridine calcium channel blocker (e.g., amlodipine or felodipine) may be considered or other antihypertensive medication doses increased. <u>Managing heart failure in special populations</u> • The combination of hydralazine/isosorbide dinitrate is recommended for African American women with moderate to severe heart failure symptoms who are on background neurohormonal inhibition. • A combination of hydralazine and isosorbide dinitrate is recommended as part of standard therapy in addition to β-blockers and ACE-inhibitors for African Americans with left ventricular systolic dysfunction and NYHA class II-IV heart failure. • As in all patients, but especially in the elderly, careful attention to volume status, the possibility of symptomatic cerebrovascular disease and the presence of postural hypotension are recommended during therapy with ACE inhibitors, β-blockers and diuretics. <u>Patients with heart failure and preserved LVEF</u> • ACE inhibitors or ARBs should be considered in this patient population. • ACE inhibitors should be considered in patients with heart failure and symptomatic atherosclerotic cardiovascular disease or diabetes and at least one other risk factor. ARBs may be used in patients who are intolerant to ACE inhibitors. • Beta-blocker treatment is recommended in patients with HF and preserved LVEF who have prior MI, hypertension, or AF. • Calcium channel blockers should be considered in patients with heart failure and preserved LVEF who have atrial fibrillation requiring ventricular rate control and intolerance to β-blockers (consider diltiazem or verapamil), symptom-limiting angina, or hypertension. • Diuretic therapy is recommended in all patients with heart failure and clinical evidence of volume overload, including those with preserved LVEF. • Treatment may begin with either a thiazide or loop diuretic. In more severe volume overload or if response to a thiazide is inadequate, treatment with a loop diuretic should be implemented. • Excessive diuresis, which may lead to orthostatic changes in blood pressure and worsening renal function, should be avoided. <u>Patients with heart failure and CAD</u> • Calcium channel blockers should be considered in patients who have angina despite optimization of β-blocker and nitrates. Amlodipine and felodipine are preferred in patients with decreased systolic function.

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	<u>Patients with heart failure and hypertension</u> • Patients with left ventricular hypertrophy or left ventricular dysfunction without left ventricular dilation should be treated to a goal blood pressure of <130/80 mm Hg. Treatment with several drugs may be necessary, including an ACE inhibitor (or ARB), a diuretic and a β-blocker or calcium channel blocker. • Patients with asymptomatic left ventricular dysfunction and left ventricular dilation and a reduced ejection fraction should receive an ACE inhibitor and a β-blocker. If blood pressure remains elevated (>130/80 mm Hg), the addition of a diuretic is recommended, followed by a calcium channel blocker or other antihypertensive agent. • If blood pressure remains >130/80 mm Hg, then the addition of a thiazide diuretic is recommended, followed by a dihydropyridine calcium channel blocker (e.g., amlodipine or felodipine) or other antihypertensive drugs. <u>Patients at risk for development of heart failure</u> • ACE inhibitors are recommended in patients who are at risk for the development of heart failure including patients with CAD, peripheral vascular disease, stroke, diabetes and another major risk factor, and patients with diabetes who smoke and have microalbuminuria. <u>Patients with asymptomatic heart failure and reduced LVEF</u> • ACE inhibitors are recommended in asymptomatic patients with reduced LVEF (<40%). • ARBs may be used in patients who are intolerant to ACE inhibitors. • Routine use of a combination of ACE inhibitors and ARBs is not recommended. • β-blocker therapy should be considered. <u>Patients with heart failure and ischemic heart disease</u> • ACE inhibitor therapy is recommended in all patients with either reduced or preserved LVEF after a MI. • Beta-blockers are recommended for the management of all patients with reduced LVEF or post-MI. • ACE inhibitor and β-blocker therapy should be initiated early (<48 hours) during hospitalization in hemodynamically stable patients who are post-MI with reduced LVEF or heart failure. • Calcium channel blockers may be considered in patients with HF who have angina despite the optimal use of β-blockers and nitrates. <u>Managing heart failure in the elderly, women and African Americans</u> • Standard regimens of ACE inhibitors and β-blockers are recommended in elderly patients with heart failure. • ACE inhibitor and β-blocker therapy are recommended in all women with heart failure and left ventricular systolic dysfunction. • ACE inhibitor and β-blocker therapy are recommended in all African American patients with heart failure and left ventricular systolic dysfunction. ARBs may be substituted in patients who are intolerant to ACE inhibitors. <u>Heart failure in patients with reduced ejection fraction</u> • ACE inhibitors are recommended in asymptomatic patients with reduced LVEF (<40%). • ARBs may be used in patients who are intolerant to ACE inhibitors. • β-blockers shown to be effective in clinical trials of patients with heart failure are recommended for patients with a LVEF ≤40%. • The combination of a β-blocker and an ACE inhibitor is recommended as routine

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	therapy for asymptomatic patients with a LVEF ≤40%. The evidence is stronger in patients with a history of MI. • β-blocker therapy is recommended for patients with a recent decompensation of heart failure after optimization of volume status and successful discontinuation of intravenous diuretics and vasoactive drugs. Whenever possible, β-blocker therapy should be initiated in the hospital setting at a low dose prior to discharge of stable patients. • β-blocker therapy is recommended in the great majority of patients with heart failure and reduced LVEF, even if there is concurrent diabetes, chronic obstructive pulmonary disease or peripheral vascular disease. Caution may be warranted in these patients. • It is recommended that β blockade be initiated at low doses and uptitrated gradually. • It is recommended that β-blocker therapy be continued in most patients experiencing a symptomatic exacerbation of heart failure during chronic maintenance treatment, unless they develop cardiogenic shock, refractory volume overload or symptomatic bradycardia. • The routine use of an ARB is not recommended in addition to an ACE inhibitor and a β-blocker in patients with a recent acute MI and reduced LVEF. • The addition of an ARB should be considered in patients with heart failure due to reduced LVEF who have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor and a β-blocker. • Administration of an aldosterone antagonist is recommended for patients with NYHA class IV (or class III, previously class IV) HF from reduced LVEF (<35%) while receiving standard therapy, including diuretics. • Diuretic therapy is recommended to restore and maintain normal volume status in patients with clinical evidence of fluid overload, generally manifested by congestive symptoms or signs of elevated filling pressures. Loop diuretics rather than thiazide-type diuretics are typically necessary to restore normal volume status in patients with heart failure. • The initial dose of diuretic may be increased as necessary to relieve congestion, and restoration of normal volume status may require multiple adjustments, especially in patients with severe fluid overload evidenced by massive edema or ascites. After a diuretic effect is achieved with loop diuretics (short acting), increasing administration frequency to twice or even three times/day will provide more diuresis with less physiologic perturbation than larger single doses. • Oral torsemide may be considered in patients in whom poor absorption of oral medication or erratic diuretic effect may be present. Particularly in patients with right-sided heart failure and refractory fluid retention despite high doses of other loop diuretics. • Intravenous administration of diuretics may be necessary to relieve congestion. • Diuretic refractoriness may represent patient nonadherence, a direct effect of diuretic use on the kidney or progression of underlying cardiac dysfunction. • Addition of chlorothiazide or metolazone, once or twice daily, to loop diuretics should be considered in patients with persistent fluid retention despite high dose loop diuretic therapy. Chronic daily use should be avoided if possible because of the potential for electrolyte shifts and volume depletion. These drugs may be used periodically (every other day or weekly) to optimize fluid management. Metolazone will generally be more potent and much longer acting in this setting and in patients with chronic renal insufficiency, so administration should be adjusted accordingly. Volume status and electrolytes must be monitored closely when multiple diuretics are used. • Careful observation for the development of side effects is recommended in patients treated with diuretics, especially when high doses or combination therapy are used. Patients should undergo routine laboratory studies and clinical

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	examination as dictated by their clinical response.
	• Patients requiring diuretic therapy to treated fluid retention associated with heart failure generally require chronic treatment, although often at lower doses than those required initially to achieve diuresis. Decreasing or discontinuing therapy may be considered in patients experiencing significant improvement in clinical status and cardiac function or in those who successfully restrict dietary sodium intake. These patients may undergo cautious weaning of diuretic dose and frequency with careful observation for recurrent fluid retention.
	• Patients and caregivers should be given education on the early signs of fluid retention and the plan for initial therapy.
	• Selected patients may be educated to adjust daily dose of diuretic in response to weight gain from fluid overload.
	
	<u>Evaluation and management of patients with acute decompensated heart failure</u>
	• Patients admitted with acute decompensated heart failure and evidence of fluid overload be treated initially with loop diuretics; usually given intravenously rather than orally. Ultrafiltration may be considered in lieu of diuretics.
	• Diuretics should be administered at doses needed to produce a rate of diuresis sufficient to achieve optimal volume status with relief of signs and symptoms of congestion, without inducing an excessively rapid reduction in intravascular volume or serum electrolytes.
	• Monitoring of daily weights, intake and output is recommended to assess clinical efficacy of diuretic therapy.
	• Careful observation for development of a variety of side effects, including renal dysfunction, electrolyte abnormalities, symptomatic hypotension and gout is recommended in patients treated with diuretics, especially when high doses or combination therapy is used.
	• Careful observation for the development of renal dysfunction is recommended in patients treated with diuretics. Patients with moderate to severe renal dysfunction and evidence of fluid retention should continue to be treated with diuretics. In the presence of severe fluid overload, renal dysfunction may improve with diuresis.
	• When congestion fails to improve in response to diuretic therapy, the following options should be considered:
	  ○ Re-evaluating the presence/absence of congestion.
	  ○ Sodium and fluid restriction.
	  ○ Increasing doses of loop diuretic.
	  ○ Continuous infusion of a loop diuretic.
	  ○ Addition of a second type of diuretic orally (metolazone or spironolactone) or intravenously (chlorothiazide).
	  ○ Ultrafiltration may be considered as well.

European Society of Cardiology: **Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (2016)**[16]	<u>Pharmacological treatments indicated in patients with symptomatic (NYHA Class II-IV) heart failure with reduced ejection fraction</u> • An ACE inhibitor is recommended, in addition to a beat-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death. • A mineralocorticoid receptor antagonist 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. • Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion. • 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.

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	• 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. • 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 heart failure with preserved ejection fraction and heart failure with mid-range ejection fraction</u> • It is recommended to screen patients with HFpEF or HFmrEF (mid-range) 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 or HFmrEF in order to alleviate symptoms and signs. <u>Recommendations for initial management of a rapid ventricular rate in patients with heart failure and atrial fibrillation in the acute or chronic setting</u> • Urgent electrical cardioversion is recommended if AF is thought to be contributing to the patient's hemodynamic compromise in order to improve the patient clinical condition. • For patients in NYHA Class IV, in addition to treatment for acute HF, an intravenous bolus of amiodarone or, in digoxin-naïve patients, an intravenous bolus of digoxin should be considered to reduce the ventricular rate. • For patients in NYHA Class I–III, a β-blocker, usually given orally, is safe and therefore is recommended as first-line treatment to control ventricular rate, provided the patient is euvolemic. • For patients in NYHA Class I–III, digoxin should be considered when ventricular rate remains high despite β-blockers or when β-blockers are not tolerated or contraindicated. • Treatment with dronedarone to improve ventricular rate control is not recommended due to safety concerns.

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	Recommendations for cardiac imaging in patients with suspected or established heart failure • Transthoracic Echocardiogram (TTE) is recommended for the assessment of myocardial structure and function in subjects with suspected HF in order to establish a diagnosis of HFrEF, HFmrEF, or HFpEF. • TTE is recommended for the assessment of LVEF in order to identify patients with HF who would be suitable for evidence-based pharmacological and device treatment recommended for HFrEF. Recommendations aiming to prevent or delay the development of overt heart failure or prevent death before the onset of symptoms • Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life. • ACE inhibitor is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction in order to prevent or delay the onset of HF and prolong life. • Beta-blocker is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction, in order to prevent or delay the onset of HF and prolong life. Pharmacological treatments indicated in patients with symptomatic 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 β-blocker is recommended, in addition to an ACE inhibitor, for patients with stable, symptomatic HFrEF to reduce the risk of HF hospitalization and death. • A mineralocorticoid receptor antagonist 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. Other pharmacological treatments recommended in selected patients with symptomatic heart failure with reduced ejection fraction • Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion. • 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. Treatments (or combinations of treatments) that may cause harm in patients with symptomatic (New York Heart Association Class II–IV) heart failure with reduced ejection fraction • Diltiazem or verapamil are not recommended in patients with HFrEF, as they increase the risk of HF worsening and HF hospitalization. • The addition of an ARB (or a renin inhibitor) to the combination of an ACE inhibitor and a mineralocorticoid receptor antagonist is not recommended in patients with HF, because of the increased risk of renal dysfunction and hyperkalemia. Not-recommended treatments of co-morbidities in patients with heart failure • Thiazolidinediones (glitazones) are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization. • NSAIDs or COX-2 inhibitors are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization.

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	Recommendations for the 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. • In patients with new-onset AHF or those with chronic, decompensated HF not receiving oral diuretics the initial recommended dose should be 20 to 40 mg intravenous furosemide (or equivalent); for those on chronic diuretic therapy, initial intravenous dose should be at least equivalent to oral dose. • It is recommended to give diuretics either as intermittent boluses or a continuous infusion, and the dose and duration should be adjusted according to the patients' symptoms and clinical status. • Inotropic agents are not recommended unless the patient is symptomatically hypotensive or hypoperfused because of safety concern.
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 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.
American Society of	Nonpharmacologic treatment

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Hypertension/ International Society of Hypertension: **Clinical Practice Guidelines for the Management of Hypertension in the Community (2014)**[18]	• In patients with hypertension that is no more severe than stage one and is not associated with evidence of abnormal cardiovascular findings or other cardiovascular risks, six to 12 months of lifestyle changes can be attempted in the hope that they may be sufficiently effective to make it unnecessary to use medicines. • It may be prudent to start treatment with drugs sooner if it is clear that the blood pressure is not responding to the lifestyle methods or if other risk factors appear. • Weight loss: In patients who are overweight or obese, weight loss is helpful in treating hypertension, diabetes, and lipid disorders. • Salt reduction: Reduction of salt intake is recommended because it can reduce blood pressure and decrease the need for medications in patients who are "salt sensitive." • Exercise: Regular aerobic exercise can help reduce blood pressure. • Alcohol consumption: Up to two drinks a day can be helpful in protecting against cardiovascular events, but greater amounts of alcohol can raise blood pressure and should therefore be discouraged. In women, alcohol should be limited to one drink a day. • Cigarette smoking: Stopping smoking will not reduce blood pressure, but since smoking by itself is such a major cardiovascular risk factor, patients must be strongly urged to discontinue this habit. <u>Drug treatment of hypertension</u> • Treatment with drugs should be started in patients with blood pressures >140/90 mm Hg in whom lifestyle treatments have not been effective. • In patients with stage two hypertension (blood pressure ≥160/100 mm Hg), drug treatment should be started immediately after diagnosis, usually with a two-drug combination, without waiting to see the effects of lifestyle changes. • For patients older than 80 years, the suggested threshold for starting treatment is at levels ≥150/90 mm Hg. Thus, the target of treatment should be <140/90 mm Hg for most patients but <150/90 mm Hg for older patients (unless these patients have chronic kidney disease or diabetes, when <140/90 mm Hg can be considered). • Most patients will require more than one drug to achieve control of their blood pressure. • In general, increase the dose of drugs or add new drugs at approximately two to three week intervals. This frequency can be faster or slower depending on the judgment of the practitioner. In general, the initial doses of drugs chosen should be at least half of the maximum dose so that only one dose adjustment is required thereafter. It is generally anticipated that most patients should reach an effective treatment regimen, whether one, two, or three drugs, within six to eight weeks. • Choice of drugs should be influenced by the age, ethnicity/race, and other clinical characteristics of the patient. • The choice of drugs will also be influenced by other conditions (e.g., diabetes and coronary disease) associated with the hypertension. Pregnancy also influences drug choice. • Long-acting drugs that need to be taken only once daily are preferred to shorter-acting drugs that require multiple doses because patients are more likely to follow a simple treatment regimen. • This guideline only makes recommendations for drug classes, not individual agents. There is an assumption, unless otherwise stated, that all drugs in a class are similar to each other. • Drug selectin when hypertension is the only or main concern: ○ For black patients of all ages, use calcium channel blocker (CCB) or thiazide diuretic as first drug, then add angiotensin receptor blocker (ARB) or angiotensin-converting enzyme (ACE) inhibitor if needed.

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	○ For white and other non-black patients <60 years of age, use ARB or ACE inhibitor as first drug, then add CCB or thiazide diuretic if needed. ○ For white and other non-black patients ≥60 years of age, use CCB or thiazide diuretic as first drug, then add ARB or ACE inhibitor if needed. • Drug selection when hypertension is associated with other conditions: ○ For patients with hypertension and diabetes, use ARB or ACE inhibitor as first drug (note, in black patients it is acceptable to start with a CCB or thiazide), then add CCB or thiazide diuretic (unless starting on CCB or thiazide in black patients) if needed. ○ For patients with hypertension and chronic kidney disease, use ARB or ACE inhibitor as first drug, then add CCB or thiazide diuretic if needed. ○ For patients with hypertension and clinical coronary artery disease, use β-blocker plus ARB or ACE inhibitor as first drugs, then add CCB or thiazide diuretic if needed. ○ For patients with hypertension and stroke history, use ACE inhibitor or ARB as first drug, then add thiazide diuretic or CCB if needed. • For patients with hypertension and heart failure, patients with h symptomatic heart failure should usually receive an ARB or ACE inhibitor plus β-blocker plus diuretic plus spironolactone regardless of blood pressure. A dihydropyridine CCB can be added if needed for blood pressure control.
Hypertension Canada: **2017 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults (2017)**[19]	<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. <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.

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	• 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>Guidelines for individuals 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> • 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>

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	• 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.
	
	<u>Treatment of hypertension in association with stroke</u>
	• BP management in acute ischemic stroke (onset to 72 hours)
	  ○ For patients with ischemic stroke not eligible for thrombolytic therapy, treatment of hypertension in the setting of acute ischemic stroke or transient ischemic attack should not be routinely undertaken. Extreme BP increases (e.g., SBP >220 mmHg or DBP >120 mmHg) may be treated to reduce the BP by approximately 15%, and not more than 25%, over the first 24 hours with gradual reduction thereafter. Avoid excessive lowering of BP because this might exacerbate existing ischemia or might induce ischemia, particularly in the setting of intracranial arterial occlusion or extracranial carotid or vertebral artery occlusion. Pharmacological agents and routes of administration should be chosen to avoid precipitous decreases in BP.
	  ○ For patients with ischemic stroke eligible for thrombolytic therapy, very high BP (>185/110 mmHg) should be treated concurrently in patients receiving thrombolytic therapy for acute ischemic stroke to reduce the risk of secondary intracranial hemorrhage.
	• 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)
	  ○ For patients with intracerebral hemorrhage (ICH) in the hyperacute phase (in the first 24 hours) SBP lowering to <140 mmHg should be avoided because of an absence of benefit (relative to a target of <180 mmHg) and some suggestion of harm.
	
	<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

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	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 • For patients with nondiabetic chronic kidney disease, target BP is <140/90 mmHg. • For patients with hypertension and proteinuric chronic kidney disease (urinary protein >500 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. • Thiazide/thiazide-like diuretics are recommended as additive antihypertensive therapy. For patients with chronic kidney disease and volume overload, loop diuretics are an alternative. • 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. • In patients with hypertension attributable to FMD-related renal artery stenosis, revascularization should be considered. • 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 2 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. Combination therapy using two first-line agents may also be considered as initial treatment of hypertension if SBP is 20 mmHg greater than target or if DBP is 10 mmHg greater than target. However, caution should be exercised in patients in whom a substantial decrease in BP is more likely or poorly tolerated (e.g., elderly patients and patients with autonomic neuropathy). • 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.
European Society of Hypertension/	The 2013 guidelines on hypertension of the European Society of Hypertension and the European Society of Cardiology follow the guidelines jointly issued by the two

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European Society of Cardiology: **2013 Guidelines for the management of arterial hypertension (2013)[20]**	societies in 2003 and 2007. <u>Treatment strategies and choice of antihypertensive drugs</u> • Diuretics (including thiazides, chlorthalidone, and indapamide), β-blockers, calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) are all suitable for the initiation and maintenance of antihypertensive treatment, either as monotherapy or in some combinations. • Some agents should be considered as the preferential choice in specific conditions because used in trials in those conditions or because of greater effectiveness in specific types of organ damage. • Initiation of antihypertensive therapy with a two-drug combination may be considered in patients with markedly high baseline blood pressure (BP) or at high cardiovascular (CV) risk. • The combination of two antagonists of the renin-angiotensin system (RAS) is not recommended and should be discouraged. • Other drug combinations should be considered and probably are beneficial in proportion to the extent of BP reduction. However, combinations that have been successfully used in trials may be preferable. • Combinations of two antihypertensive drugs at fixed doses in a single tablet may be recommended and favored, because reducing the number of daily pills improves adherence, which is low in patients with hypertension. <u>Treatment strategies in white-coat and masked hypertension</u> • In white-coat hypertensives without additional risk factors, therapeutic intervention may be limited to lifestyle changes only, but this decision should be accompanied by close follow-up. • In white-coat hypertensives with a higher CV risk because of metabolic derangements or asymptomatic organ damage, drug treatment may be considered in addition to lifestyle changes. • In masked hypertension, both lifestyle measures and antihypertensive drug treatment should be considered, because this type of hypertension has been consistently found to have a CV risk very close to that of in- and out-of-office hypertension. <u>Antihypertensive treatment strategies in the elderly</u> • In elderly hypertensives with SBP ≥160 mmHg there is solid evidence to recommend reducing SBP to between 150 and 140 mmHg. • In fit elderly patients <80 years old antihypertensive treatment may be considered at SBP values ≥140 mmHg with a target SBP <140 mmHg if treatment is well tolerated. • In individuals older than 80 years with an initial SBP ≥160 mmHg, it is recommended to reduce SBP to between 150 and 140 mmHg, provided they are in good physical and mental conditions. • In frail elderly patients, it is recommended to leave decisions on antihypertensive therapy to the treating physician, and based on monitoring of the clinical effects of treatment. • Continuation of well-tolerated antihypertensive treatment should be considered when a treated individual becomes an octogenarian. • All hypertensive agents are recommended and can be used in the elderly, although diuretics and calcium antagonists may be preferred in isolated systolic hypertension. <u>Treatment strategies in hypertensive women</u> • Hormone therapy and selective estrogen receptor modulators are not

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	recommended and should not be used for primary or secondary prevention of CVD. • If treatment of younger perimenopausal women is considered for severe menopausal symptoms, the benefits should be weighed against potential risks. • Drug treatment of severe hypertension in pregnancy (SBP >160 mmHg or DBP >110 mmHg) is recommended. • Drug treatment may also be considered in pregnant women with persistent elevation of BP ≥150/95 mmHg, and in those with BP ≥140/90 mmHg in the presence of gestational hypertension, subclinical organ damage or symptoms. • In women at high risk of pre-eclampsia, provided they are at low risk of gastrointestinal hemorrhage, treatment with low dose aspirin from 12 weeks until delivery may be considered. • In women with child-bearing potential RAS blockers are not recommended and should be avoided. • Methyldopa, labetalol, and nifedipine should be considered preferential antihypertensive drugs in pregnancy. Intravenous labetalol or infusion of nitroprusside should be considered in case of emergency (pre-eclampsia). <u>Treatment strategies in patients with diabetes</u> • While initiation of antihypertensive drug treatment in diabetic patients whose SBP is ≥160 mmHg is mandatory, it is strongly recommended to start drug treatment also when SBP is ≥140 mmHg. • A SBP goal <140 mmHg is recommended in patients with diabetes. • The DBP target in patients with diabetes is recommended to be <85 mmHg. • All classes of antihypertensive agents are recommended and can be used in patients with diabetes; RAS blockers may be preferred, especially in the presence of proteinuria or microalbuminuria. • It is recommended that individual drug choice takes comorbidities into account. • Simultaneous administration of two blockers of the RAS is not recommended and should be avoided in patients with diabetes <u>Treatment strategies in hypertensive patients with metabolic syndrome</u> • Lifestyle changes, particularly weight loss and physical exercise, are to be recommended to all individuals with the metabolic syndrome. These interventions improve not only BP, but the metabolic components of the syndrome and delay diabetes onset. • As the metabolic syndrome can be considered a 'pre-diabetic' state, antihypertensive agents potentially improving or at least not worsening insulin sensitivity, such as RAS blockers and calcium antagonists, should be considered as the preferred drugs. Beta-blockers (with the exception of vasodilating β-blockers) and diuretics should be considered only as additional drugs, preferably in association with a potassium-sparing agent. • It is recommended to prescribe antihypertensive drugs with particular care in hypertensive patients with metabolic disturbances when BP is ≥140/90 mmHg after a suitable period of lifestyle changes, and to maintain BP <140/90 mmHg. • BP lowering drugs are not recommended in individuals with metabolic syndrome and high normal BP. <u>Therapeutic strategies in hypertensive patients with nephropathy</u> • Lowering SBP to <140 mmHg should be considered. • When overt proteinuria is present, SBP values <130 mmHg may be considered, provided that changes in eGFR are monitored. • RAS blockers are more effective in reducing albuminuria than other antihypertensive agents, and are indicated in hypertensive patients in the presence of microalbuminuria or overt proteinuria.

Clinical Guideline	Recommendations
	• Reaching BP goals usually requires combination therapy, and it is recommended to combine RAS blockers with other antihypertensive agents. • Combination of two RAS blockers, though potentially more effective in reducing proteinuria, is not recommended. • Aldosterone antagonists cannot be recommended in chronic kidney disease (CKD), especially in combination with a RAS blocker, because of the risk of excessive reduction in renal function and of hyperkalemia. <u>Therapeutic strategies in hypertensive patients with cerebrovascular disease</u> • It is not recommended to intervene with BP-lowering therapy during the first week after acute stroke irrespective of BP level, although clinical judgement should be used in the face of very high SBP values. • Antihypertensive treatment is recommended in hypertensive patients with a history of stroke or transient ischemic attack (TIA), even when initial SBP is in the 140 to 159 mmHg range. • In hypertensive patients with a history of stroke or TIA, a SBP goal of <140 mmHg should be considered. • In elderly hypertensives with previous stroke or TIA, SBP values for intervention and goal may be considered to be somewhat higher. • All drug regimens are recommended for stroke prevention, provided that BP is effectively reduced. <u>Therapeutic strategies in hypertensive patients with heart disease</u> • In hypertensive patients with CHD, a SBP goal <140 mmHg should be considered. • In hypertensive patients with a recent myocardial infarction, β-blockers are recommended. In case of other CHD all antihypertensive agents can be used, but β-blockers and calcium antagonists are to be preferred for symptomatic reasons (angina). • Diuretics, β-blockers, ACE inhibitors, angiotensin receptor blockers, and/or mineralocorticoid receptor antagonists are recommended in patients with heart failure or severe left ventricular (LV) dysfunction to reduce mortality and hospitalization. • In patients with heart failure and preserved ejection fraction (EF), there is no evidence that antihypertensive therapy per se or any particular drug is beneficial. However, in these patients, as well as in patients with hypertension and systolic dysfunction, lowering SBP to around 140 mmHg should be considered. Treatment guided by relief of symptoms (congestion with diuretics, high heart rate with β-blockers, etc.) should also be considered. • ACE inhibitors and angiotensin receptor blockers (and β-blockers and mineralocorticoid receptor antagonists if heart failure coexists) should be considered as antihypertensive agents in patients at risk of new or recurrent atrial fibrillation. • It is recommended that all patients with left ventricular hypertrophy (LVH) receive antihypertensive agents. • In patients with LVH, initiation of treatment with one of the agents that have shown a greater ability to regress LVH should be considered, i.e. ACE inhibitors, angiotensin receptor blockers, and calcium antagonists. <u>Therapeutic strategies in hypertensive patients with atherosclerosis, arteriosclerosis, and peripheral artery disease (PAD)</u> • In the presence of carotid atherosclerosis, prescription of calcium antagonists and ACE inhibitors should be considered as these agents have shown a greater efficacy in delaying atherosclerosis progression than diuretics and β-blockers. • In hypertensive patients with a pulse wave velocity above 10 m/s, all

Clinical Guideline	Recommendations
	antihypertensive drugs should be considered provided that a BP reduction to <140/90 mmHg is consistently achieved. • Antihypertensive therapy is recommended in hypertensive patients with PAD to achieve a goal of <140/90 mmHg, because of their high risk of myocardial infarction, stroke, heart failure, and CV death. ○ Though a careful follow up is necessary, β-blockers may be considered for the treatment of arterial hypertension in patients with PAD, since their use does not appear to be associated with exacerbation of PAD symptoms.

National Institute for Health and Clinical Excellence: **Hypertension in adults: diagnosis and management (2011)**[21]
 	
Reaffirmed Nov 2016
	Choosing antihypertensive drug treatment
	• 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 people ≥80 years of age the same antihypertensive drug treatment as people aged 55 to 80 years, taking into account any comorbidities.
	• Offer antihypertensive drug treatment to women of child-bearing potential in line with the recommendations on Management of pregnancy with chronic hypertension and Breastfeeding in 'Hypertension in pregnancy' (NICE clinical guideline 107).
	
	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). 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 step one antihypertensive (ACE inhibitor, ARB) with a calcium channel blocker (CCB) to patients >55 years of age and to black patients of African or Caribbean family origin 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 chlorthalidone (12.5 to 25.0 mg once daily) or indapamide (1.5 mg modified-release once daily or 2.5 mg once daily) in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide.
	• For patients who are already receiving treatment with bendroflumethiazide or hydrochlorothiazide and whose blood pressure is stable and well controlled, continue treatment as is.
	• β-blockers are not a preferred initial therapy for hypertension; however, β-blockers may be considered in younger patients, particularly:
	  ○ Patients with an intolerance or contraindication to ACE inhibitors and ARBs.
	  ○ Women of child-bearing potential.
	  ○ People with evidence of increased sympathetic drive.
	• If treatment is initiated with a β-blocker and a second antihypertensive is required, add a CCB over a thiazide-like diuretic to reduce the risk of developing diabetes.
	
	Step two treatment
	• If blood pressure is not controlled with a step one antihypertensive, offer a step two treatment with a CCB in combination with an ACE inhibitor or an ARB.
	• If a CCB is not appropriate or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic.

Clinical Guideline	Recommendations

	• For black patients of African or Caribbean family origin, consider an ARB in preference to an ACE inhibitor, in combination with a CCB.
	
	Step three treatment
	• Before considering step three treatment, review medication to ensure step two treatment is at optimal or best tolerated doses.
	• If three drugs are required to control blood pressure, the combination of an ACE inhibitor or ARB, CCB, and thiazide-like diuretic should be utilized.
	
	Step four treatment
	• Regard clinic blood pressure that remains >140/90 mmHg after treatment with the optimal or best tolerated doses of an ACE inhibitor or an ARB plus a CCB plus a diuretic as resistant hypertension, and consider adding a fourth antihypertensive drug and/or seeking expert advice.
	• For treatment of resistant hypertension at step four:
	  ○ Consider further diuretic therapy with low-dose spironolactone (25 mg once daily) if the blood potassium level is 4.5 mmol/l or lower. Use particular caution in people with a reduced estimated glomerular filtration rate because they have an increased risk of hyperkalemia.
	  ○ Consider higher-dose thiazide-like diuretic treatment if the blood potassium level is higher than 4.5 mmol/l.
	• If further diuretic therapy for resistant hypertension is not tolerated or is contraindicated or ineffective, consider an α-blocker or β-blocker.

International Society on Hypertension in Blacks: **Management of High Blood Pressure in Blacks (2010)**[22]	• 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**	Blood pressure management in chronic kidney disease (CKD) non-dialysis (ND) patients without diabetes mellitus • The Work Group recommends that non-diabetic adults with CKD ND and urine albumin excretion <30 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >140 mm Hg systolic or >90 mm Hg diastolic be treated with blood pressure -lowering drugs to maintain a blood pressure that is consistently ≤140 mm Hg systolic and ≤90 mm Hg diastolic. • The Work Group suggests that non-diabetic adults with CKD ND and urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*) whose office

Clinical Guideline	Recommendations
(2012)[23]	blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with BP-lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic. • The Work Group suggests that non-diabetic adults with CKD ND and urine albumin excretion >300 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with blood pressure -lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤ 80 mm Hg diastolic. • The Work Group suggests that an angiotensin receptor blocker (ARB) or angiotensin converting enzyme inhibitor (ACE-I) be used in non-diabetic adults with CKD ND and urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*) in whom treatment with blood pressure -lowering drugs is indicated. • The Work Group recommends that an ARB or ACE-I be used in non-diabetic adults with CKD ND and urine albumin excretion >300 mg per 24 hours (or equivalent*) in whom treatment with blood pressure -lowering drugs is indicated. <u>Blood pressure management in CKD ND patients with diabetes mellitus</u> • The Work Group recommends that adults with diabetes and CKD ND with urine albumin excretion <30 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >140 mm Hg systolic or >90 mm Hg diastolic be treated with BP-lowering drugs to maintain a blood pressure that is consistently ≤140 mm Hg systolic and ≤90 mm Hg diastolic. • The Work Group suggests that adults with diabetes and CKD ND with urine albumin excretion >30 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with BP-lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic. • The Work Group suggests that an ARB or ACE-I be used in adults with diabetes and CKD ND with urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*). • The Work Group recommends that an ARB or ACE-I be used in adults with diabetes and CKD ND with urine albumin excretion >300 mg per 24 hours (or equivalent*). <u>Blood pressure management in kidney transplant recipients (non–dialysis-dependent CKD of any stage with a kidney transplant [CKD T])</u> • The Work Group suggests that adult kidney transplant recipients whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic, irrespective of the level of urine albumin excretion. • In adult kidney transplant recipients, choose a blood pressure -lowering agent after taking into account the time after transplantation, use of calcineurin inhibitors, presence or absence of persistent albuminuria, and other co morbid conditions. <u>Blood pressure management in children with CKD ND</u> • The Work Group recommends that in children with CKD ND, blood pressure -lowering treatment is started when blood pressure is consistently above the 90th percentile for age, sex, and height. • The Work Group suggests that in children with CKD ND (particularly those with proteinuria), blood pressure is lowered to consistently achieve systolic and diastolic readings less than or equal to the 50th percentile for age, sex, and height, unless achieving these targets is limited by signs or symptoms of hypotension. • The Work Group suggests that an ARB or ACE-I be used in children with CKD

Clinical Guideline	Recommendations
	ND in whom treatment with blood pressure -lowering drugs is indicated, irrespective of the level of proteinuria. Blood pressure management in elderly persons with CKD ND • Tailor blood pressure treatment regimens in elderly patients with CKD ND by carefully considering age, co-morbidities and other therapies, with gradual escalation of treatment and close attention to adverse events related to blood pressure treatment, including electrolyte disorders, acute deterioration in kidney function, orthostatic hypotension and drug side effects. *Approximate equivalents for albumin excretion rate per 24 hours is expressed as protein excretion rate per 24 hours, albumin/creatinine ratio, protein/creatinine ratio, and protein reagent strip results.
American Diabetes Association: **Standards of Medical Care in Diabetes (2017)**[24]	Hypertension/blood pressure control • Blood pressure should be measured at every routine visit. Patients found to have elevated blood pressure should have blood pressure confirmed on a separate day. • Most patients with diabetes and hypertension should be treated to a systolic blood pressure goal of <140 mmHg and a diastolic blood pressure goal of <90 mmHg. • Lower systolic and diastolic blood pressure targets, such as 130/80 mmHg, may be appropriate for individuals at high risk of cardiovascular disease, if they can be achieved without undue treatment burden. • In pregnant patients with diabetes and chronic hypertension, blood pressure targets of 120 to 160/80 to 105 mmHg are suggested in the interest of optimizing long-term maternal health and minimizing impaired fetal growth. • Patients with confirmed office-based blood pressure >140/90 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). 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. • For patients with blood pressure >120/80 mmHg, lifestyle intervention consists of weight loss if overweight or obese; a Dietary Approaches to Stop Hypertension–style dietary pattern including reducing sodium and increasing potassium intake; moderation of alcohol intake; and increased physical activity. Coronary heart disease • In asymptomatic patients, routine screening for coronary artery disease is not recommended as it does not improve outcomes as long as atherosclerotic cardiovascular disease risk factors are treated. • Consider investigations for coronary artery disease in the presence of any of the

Clinical Guideline	Recommendations
	following: atypical cardiac symptoms (e.g., unexplained dyspnea, chest discomfort); signs or symptoms of associated vascular disease including carotid bruits, transient ischemic attack, stroke, claudication, or peripheral arterial disease; or electrocardiogram abnormalities (e.g., Q waves). • In patients with known atherosclerotic cardiovascular disease, use aspirin and statin therapy (if not contraindicated) and consider ACE inhibitor therapy to reduce the risk of cardiovascular events. • In patients with prior myocardial infarction, β-blockers should be continued for at least two years after the event. • In patients with symptomatic heart failure, thiazolidinedione treatment should not be used. • In patients with type 2 diabetes with stable congestive heart failure, metformin may be used if estimated glomerular filtration remains >30 mL/min but should be avoided in unstable or hospitalized patients with congestive heart failure. <u>Diabetic 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, in all patients with type 2 diabetes, and in all patients with comorbid hypertension. • Optimize glucose control to reduce the risk or slow the progression of diabetic kidney disease. • Optimize blood pressure control to reduce the risk or slow the progression of diabetic kidney disease. • For people with nondialysis-dependent diabetic kidney disease, dietary protein intake should be approximately 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. • 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) B 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 or changes in potassium when ACE inhibitors, angiotensin receptor blockers, or diuretics are used. • Continued monitoring of urinary albumin–to–creatinine ratio in patients with albuminuria treated with an ACE inhibitor or an angiotensin receptor blocker is reasonable to assess the response to treatment and progression of diabetic kidney disease. • An ACE inhibitor or an angiotensin receptor blocker is not recommended for the primary prevention of diabetic kidney disease 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. • When estimated glomerular filtration rate is <60 mL/min/1.73 m^2, evaluate and manage potential complications of chronic kidney disease. • Patients should be referred for evaluation for renal replacement treatment if they have an estimated glomerular filtration rate <30 mL/min/1.73 m^2. • Promptly refer to a physician experienced in the care of kidney disease for uncertainty about the etiology of kidney disease, difficult management issues, and rapidly progressing kidney disease.
American Association for the Study of Liver Diseases: **Management of**	<u>Treatment of ascites</u> • First line treatment of patients with cirrhosis and ascites consists of sodium restriction (88 mmol/day [2,000 mg/day]) and diuretics (oral spironolactone with or without oral furosemide).

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Adult Patients with Ascites Due to Cirrhosis: Update 2012 (2012)[25] **[Reaffirmed Oct 2014]**	• Fluid restriction is not necessary unless serum sodium is <125 mmol/L. • Vasopressin antagonists may improve serum sodium in patients with cirrhosis and ascites. However their use does not currently appear justified in view of their expense, potential risks, and lack of evidence of efficacy in clinically meaningful outcomes. • An initial therapeutic abdominal paracentesis should be performed in patients with tense ascites. Sodium restriction and oral diuretics should then be initiated. • Diuretic-sensitive patients should preferably be treated with sodium restriction and oral diuretics rather than with serial paracentesis. • Use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers in patients with cirrhosis and ascites may be harmful and must be carefully considered in each patient, monitoring blood pressure and renal function. • The use of nonsteroidal anti-inflammatory drugs should be avoided in patients with cirrhosis and ascites, except in special circumstances. • Liver transplantation should be considered in patients with cirrhosis and ascites.
Endocrine Society: **The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment (2016)[26]**	• 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. • 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.
American Association of Clinical Endocrinologists: **Medical Guidelines for Clinical Practice for the Diagnosis and Treatment of Hypertension (2006)[27]**	<u>Primary hyperaldosteronism</u> • Surgery is the preferred treatment modality for patients with unilateral adenomas. • Spironolactone may be used in lieu of surgery in female or elderly patients with small adenomas or hyperplasias. Since male patients may experience erectile dysfunction and gynecomastia with spironolactone therapy, a trial of eplerenone may be considered. • Glucocorticoid-remediable aldosteronism is treated with glucocorticoids.

*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[1-5]

Indication(s)	Single Entity Agents		Combination Products
	Eplerenone	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		✔	
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)		✔	

*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.

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					
Eplerenone	69	50	Liver, extensive (% not reported)	Renal (67) Feces (32)	3 to 6
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	Imidazoles	Certain azole antifungal agents may decrease the elimination

Generic Name(s)	Interaction	Mechanism
receptor antagonists (eplerenone)		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 (eplerenone)	Macrolides	Macrolides 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 (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).
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. The boxed warning for the mineralocorticoid (aldosterone) receptor antagonists are listed in Tables 7 and 8.

Table 6. Adverse Drug Events (%) Reported with the Mineralocorticoid (Aldosterone) Receptor Antagonists[1-5]

Adverse Events	Single Entity Agents		Combination Products
	Eplerenone	Spironolactone	Spironolactone and HCTZ
Cardiovascular			
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	-	✔	✔
Cholestatic toxicity	-	✔	✔
Constipation	-	-	✔
Cramping	-	✔	✔

Adverse Events	Single Entity Agents		Combination Products
	Eplerenone	Spironolactone	Spironolactone and HCTZ
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	≤40	≤40
Hypertriglyceridemia	<15	-	-
Hyponatremia	2	✔	✔
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

Table 7. Boxed Warning for Spironolactone[3]

WARNING
Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. Spironolactone should be used only in those conditions described under Indications and Usages. Unnecessary use of this drug should be avoided.

Table 8. Boxed Warning for Spironolactone and HCTZ[5]

WARNING
Spironolactone, an ingredient of Aldactazide®, has been shown to be a tumorigen in chronic toxicity studies in rats. Aldactazide® should be used only in those conditions described under Indications and Usage. Unnecessary use of this drug should be avoided. Fixed-dose combination drugs are not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension and edema is not static but must be reevaluated as conditions in each patient warrant.

VII. Dosing and Administration

The usual dosing regimens for the mineralocorticoid (aldosterone) receptor antagonists are listed in Table 9.

Table 9. Usual Dosing Regimens for the Mineralocorticoid (Aldosterone) Receptor Antagonists[1-5]

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
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 Heart failure (Severe NYHA function class III to IV) Tablet: initial, 25 mg once daily; maintenance, 25 mg every other day to 50 mg once daily Hypertension 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	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
	days 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 10.

Table 10. 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.[28] (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.[29] (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.[30] (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.[31] (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.[32] (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.[33] (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.[34] (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.[35] (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.[36] (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.[37] (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.[38] (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.[39] (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.[40] (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.[41] (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.[42] (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.[43] (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.[44] (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.[45] (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.[46] (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.[47] (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.[48] (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.[49] (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.[50] (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.[51] (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.[52] (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.[53] (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.[54] (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.[55] (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.[56] (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.[57] (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.[58] (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.[59] (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.[60] (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.[61] (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.[62] (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.[63] (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.[64] (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.[65] (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.[66] (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.[67] (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.[68] (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.[69] (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.[70] (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.[71] (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.[72] (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.[73] (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.[74] (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.[75]	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.[76] (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.[77] (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.[78] (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.[79] (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
Bomback et al.[80] (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 were treated with ACE inhibitors	N=21 8 weeks	Primary: Change in 24-hour ambulatory blood pressure, changes in office blood pressure, nocturnal blood pressure, and urine albumin: creatinine ratio Secondary: Not reported	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 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.[81] (2015) PATHWAY-2 Twelve weeks of once daily	DB, PC, XO Patients 18 to 79 years of age with seated clinic SBP ≥ 140 mmHg (or ≥135	N=335 12 months	Primary: Average home SBP, recorded in the morning and the evening in triplicate, on four	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;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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	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)		consecutive days before study visits Secondary: Clinic SBP, BP control rates, adverse events	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.[82] (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	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	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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	≥140 mm Hg and/or DBP ≥90 mm Hg (on antihypertensive therapy)			Secondary: Not reported
Miscellaneous				
Pitt et al.[83] (2003) 4E-Left Ventricular Hypertrophy Study Eplerenone 200 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	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
enalapril 40 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.			Hg), change in urine albumin creatinine ratio	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). 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.[84] (2006) Candesartan 8 mg in addition to spironolactone 25 mg QD for 6 months, after 6 months of candesartan monotherapy	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(combination group) vs candesartan 8 mg daily for 12 months				
Edwards et al.[85] (2009) Spironolactone 25 mg QD vs placebo Study medications were added to existing ACE inhibitor or ARB therapy.	DB, PC, RCT Patients 18 to 80 years of age with stage 2 and 3 chronic kidney disease with controlled blood pressure (mean daytime ambulatory blood pressure <130/85 mm Hg) on and ACE inhibitors or ARB for 6 months	N=115 36 weeks	Primary: Change in left ventricular mass and arterial stiffness measured Secondary: Aortic distensibility, Aug AIx, blood pressure, and albuminuria	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. 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, 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).[86]

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 Mineralocorticoid (Aldosterone) Receptor Antagonists

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Eplerenone	tablet	Inspra®*	$$$$$	$$$$
Spironolactone	tablet	Aldactone®*	$$	$
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 are approved for the treatment of hypertension.[3-5] 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.[4] 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 available as single entity agents, as well as in combination with hydrochlorothiazide as a fixed-dose combination product. All of the mineralocorticoid (aldosterone) receptor antagonist products are available in a generic formulation.

There are several national and international guidelines that provide recommendations regarding the use of the mineralocorticoid (aldosterone) receptor antagonists.[6-27] 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).[14-16] 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.[17-23] 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.[17-23] Most patients will require more than one antihypertensive agent to achieve blood pressure goals.[17-23]

For the treatment of cirrhosis and ascites, spironolactone is recommended as first line therapy in addition to sodium restriction.[25] 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.[26,27]

Eplerenone and spironolactone have been shown to reduce cardiovascular morbidity and mortality in patients with heart failure when added to standard therapy.[39-44,46-51] These agents have also been shown to effectively lower blood pressure.[62-82] 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.[66] Most patients will require more than one antihypertensive agent to achieve blood pressure goals.[17-23] The use of a fixed-dose combination product may simplify the treatment regimen and improve adherence.[19-20,23,86] 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.[28-38]

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).[1-5]

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.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Renin Inhibitors
AHFS Class 243240
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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. There are no generic renin inhibitor products currently available; however, hydrochlorothiazide is available generically. This class was last reviewed in August 2015.

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®	none
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

Clinical Guideline	Recommendations
	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.
American Society of Hypertension/ International Society of Hypertension: **Clinical Practice Guidelines for the Management of Hypertension in the Community (2014)**[10]	Nonpharmacologic treatment • In patients with hypertension that is no more severe than stage one and is not associated with evidence of abnormal cardiovascular findings or other cardiovascular risks, six to 12 months of lifestyle changes can be attempted in the hope that they may be sufficiently effective to make it unnecessary to use medicines. • It may be prudent to start treatment with drugs sooner if it is clear that the blood pressure is not responding to the lifestyle methods or if other risk factors appear. • Weight loss: In patients who are overweight or obese, weight loss is helpful in treating hypertension, diabetes, and lipid disorders. • Salt reduction: Reduction of salt intake is recommended because it can reduce blood pressure and decrease the need for medications in patients who are "salt sensitive." • Exercise: Regular aerobic exercise can help reduce blood pressure. • Alcohol consumption: Up to two drinks a day can be helpful in protecting against cardiovascular events, but greater amounts of alcohol can raise blood pressure and should therefore be discouraged. In women, alcohol should be limited to one drink a day. • Cigarette smoking: Stopping smoking will not reduce blood pressure, but since smoking by itself is such a major cardiovascular risk factor, patients must be strongly urged to discontinue this habit. Drug treatment of hypertension • Treatment with drugs should be started in patients with blood pressures >140/90 mm Hg in whom lifestyle treatments have not been effective. • In patients with stage two hypertension (blood pressure ≥160/100 mm Hg), drug

Clinical Guideline	Recommendations

	treatment should be started immediately after diagnosis, usually with a two-drug combination, without waiting to see the effects of lifestyle changes.
	• For patients older than 80 years, the suggested threshold for starting treatment is at levels ≥150/90 mm Hg. Thus, the target of treatment should be <140/90 mm Hg for most patients but <150/90 mm Hg for older patients (unless these patients have chronic kidney disease or diabetes, when <140/90 mm Hg can be considered).
	• Most patients will require more than one drug to achieve control of their blood pressure.
	• In general, increase the dose of drugs or add new drugs at approximately two to three week intervals. This frequency can be faster or slower depending on the judgment of the practitioner. In general, the initial doses of drugs chosen should be at least half of the maximum dose so that only one dose adjustment is required thereafter. It is generally anticipated that most patients should reach an effective treatment regimen, whether one, two, or three drugs, within six to eight weeks.
	• Choice of drugs should be influenced by the age, ethnicity/race, and other clinical characteristics of the patient.
	• The choice of drugs will also be influenced by other conditions (e.g., diabetes and coronary disease) associated with the hypertension. Pregnancy also influences drug choice.
	• Long-acting drugs that need to be taken only once daily are preferred to shorter-acting drugs that require multiple doses because patients are more likely to follow a simple treatment regimen.
	• This guideline only makes recommendations for drug classes, not individual agents. There is an assumption, unless otherwise stated, that all drugs in a class are similar to each other.
	• Drug selectin when hypertension is the only or main concern:
	  ○ For black patients of all ages, use calcium channel blocker (CCB) or thiazide diuretic as first drug, then add angiotensin receptor blocker (ARB) or angiotensin-converting enzyme (ACE) inhibitor if needed.
	  ○ For white and other non-black patients <60 years of age, use ARB or ACE inhibitor as first drug, then add CCB or thiazide diuretic if needed.
	  ○ For white and other non-black patients ≥60 years of age, use CCB or thiazide diuretic as first drug, then add ARB or ACE inhibitor if needed.
	• Drug selection when hypertension is associated with other conditions:
	  ○ For patients with hypertension and diabetes, use ARB or ACE inhibitor as first drug (note, in black patients it is acceptable to start with a CCB or thiazide), then add CCB or thiazide diuretic (unless starting on CCB or thiazide in black patients) if needed.
	  ○ For patients with hypertension and chronic kidney disease, use ARB or ACE inhibitor as first drug, then add CCB or thiazide diuretic if needed.
	  ○ For patients with hypertension and clinical coronary artery disease, use β-blocker plus ARB or ACE inhibitor as first drugs, then add CCB or thiazide diuretic if needed.
	  ○ For patients with hypertension and stroke history, use ACE inhibitor or ARB as first drug, then add thiazide diuretic or CCB if needed.
	• For patients with hypertension and heart failure, patients with h symptomatic heart failure should usually receive an ARB or ACE inhibitor plus β-blocker plus diuretic plus spironolactone regardless of blood pressure. A dihydropyridine CCB can be added if needed for blood pressure control.

Hypertension Canada: **2017 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of**	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

Clinical Guideline	Recommendations

Hypertension in Adults (2017)[11]	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.
	
	<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>Guidelines for individuals 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

Clinical Guideline	Recommendations
	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. Treatment of hypertension in association with stroke • BP management in acute ischemic stroke (onset to 72 hours) ○ For patients with ischemic stroke not eligible for thrombolytic therapy, treatment of hypertension in the setting of acute ischemic stroke or transient ischemic attack should not be routinely undertaken. Extreme BP increases

Clinical Guideline	Recommendations
	(e.g., SBP >220 mmHg or DBP >120 mmHg) may be treated to reduce the BP by approximately 15%, and not more than 25%, over the first 24 hours with gradual reduction thereafter. Avoid excessive lowering of BP because this might exacerbate existing ischemia or might induce ischemia, particularly in the setting of intracranial arterial occlusion or extracranial carotid or vertebral artery occlusion. Pharmacological agents and routes of administration should be chosen to avoid precipitous decreases in BP. ○ For patients with ischemic stroke eligible for thrombolytic therapy, very high BP (>185/110 mmHg) should be treated concurrently in patients receiving thrombolytic therapy for acute ischemic stroke to reduce the risk of secondary intracranial hemorrhage. • 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) ○ For patients with intracerebral hemorrhage (ICH) in the hyperacute phase (in the first 24 hours) SBP lowering to <140 mmHg should be avoided because of an absence of benefit (relative to a target of <180 mmHg) and some suggestion of harm. <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> • For patients with nondiabetic chronic kidney disease, target BP is <140/90 mmHg. • For patients with hypertension and proteinuric chronic kidney disease (urinary protein >500 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. • Thiazide/thiazide-like diuretics are recommended as additive antihypertensive therapy. For patients with chronic kidney disease and volume overload, loop diuretics are an alternative. • 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,

Clinical Guideline	Recommendations
	progressive renal function loss, and acute pulmonary edema. • Patients with confirmed renal fibromuscular dysplasia (FMD) should be referred to a hypertension specialist. • In patients with hypertension attributable to FMD-related renal artery stenosis, revascularization should be considered. • 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 2 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. Combination therapy using two first-line agents may also be considered as initial treatment of hypertension if SBP is 20 mmHg greater than target or if DBP is 10 mmHg greater than target. However, caution should be exercised in patients in whom a substantial decrease in BP is more likely or poorly tolerated (e.g., elderly patients and patients with autonomic neuropathy). • 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.
European Society of Hypertension/ European Society of Cardiology: **2013 Guidelines for the management of arterial hypertension (2013)**[12]	The 2013 guidelines on hypertension of the European Society of Hypertension and the European Society of Cardiology follow the guidelines jointly issued by the two societies in 2003 and 2007. Treatment strategies and choice of antihypertensive drugs • Diuretics (including thiazides, chlorthalidone, and indapamide), β-blockers, calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) are all suitable for the initiation and maintenance of antihypertensive treatment, either as monotherapy or in some combinations. • Some agents should be considered as the preferential choice in specific conditions because used in trials in those conditions or because of greater effectiveness in specific types of organ damage. • Initiation of antihypertensive therapy with a two-drug combination may be considered in patients with markedly high baseline blood pressure (BP) or at high cardiovascular (CV) risk. • The combination of two antagonists of the renin-angiotensin system (RAS) is not recommended and should be discouraged. • Other drug combinations should be considered and probably are beneficial in proportion to the extent of BP reduction. However, combinations that have been successfully used in trials may be preferable. • Combinations of two antihypertensive drugs at fixed doses in a single tablet may be recommended and favored, because reducing the number of daily pills improves adherence, which is low in patients with hypertension. Treatment strategies in white-coat and masked hypertension • In white-coat hypertensives without additional risk factors, therapeutic

Clinical Guideline	Recommendations
	intervention may be limited to lifestyle changes only, but this decision should be accompanied by close follow-up. • In white-coat hypertensives with a higher CV risk because of metabolic derangements or asymptomatic organ damage, drug treatment may be considered in addition to lifestyle changes. • In masked hypertension, both lifestyle measures and antihypertensive drug treatment should be considered, because this type of hypertension has been consistently found to have a CV risk very close to that of in- and out-of-office hypertension. <u>Antihypertensive treatment strategies in the elderly</u> • In elderly hypertensives with SBP ≥160 mmHg there is solid evidence to recommend reducing SBP to between 150 and 140 mmHg. • In fit elderly patients <80 years old antihypertensive treatment may be considered at SBP values ≥140 mmHg with a target SBP <140 mmHg if treatment is well tolerated. • In individuals older than 80 years with an initial SBP ≥160 mmHg, it is recommended to reduce SBP to between 150 and 140 mmHg, provided they are in good physical and mental conditions. • In frail elderly patients, it is recommended to leave decisions on antihypertensive therapy to the treating physician, and based on monitoring of the clinical effects of treatment. • Continuation of well-tolerated antihypertensive treatment should be considered when a treated individual becomes an octogenarian. • All hypertensive agents are recommended and can be used in the elderly, although diuretics and calcium antagonists may be preferred in isolated systolic hypertension. <u>Treatment strategies in hypertensive women</u> • Hormone therapy and selective estrogen receptor modulators are not recommended and should not be used for primary or secondary prevention of CVD. • If treatment of younger perimenopausal women is considered for severe menopausal symptoms, the benefits should be weighed against potential risks. • Drug treatment of severe hypertension in pregnancy (SBP >160 mmHg or DBP >110 mmHg) is recommended. • Drug treatment may also be considered in pregnant women with persistent elevation of BP ≥150/95 mmHg, and in those with BP ≥140/90 mmHg in the presence of gestational hypertension, subclinical organ damage or symptoms. • In women at high risk of pre-eclampsia, provided they are at low risk of gastrointestinal hemorrhage, treatment with low dose aspirin from 12 weeks until delivery may be considered. • In women with child-bearing potential RAS blockers are not recommended and should be avoided. • Methyldopa, labetalol, and nifedipine should be considered preferential antihypertensive drugs in pregnancy. Intravenous labetalol or infusion of nitroprusside should be considered in case of emergency (pre-eclampsia). <u>Treatment strategies in patients with diabetes</u> • While initiation of antihypertensive drug treatment in diabetic patients whose SBP is ≥160 mmHg is mandatory, it is strongly recommended to start drug treatment also when SBP is ≥140 mmHg. • A SBP goal <140 mmHg is recommended in patients with diabetes. • The DBP target in patients with diabetes is recommended to be <85 mmHg. • All classes of antihypertensive agents are recommended and can be used in

Clinical Guideline	Recommendations
	patients with diabetes; RAS blockers may be preferred, especially in the presence of proteinuria or microalbuminuria. • It is recommended that individual drug choice takes comorbidities into account. • Simultaneous administration of two blockers of the RAS is not recommended and should be avoided in patients with diabetes <u>Treatment strategies in hypertensive patients with metabolic syndrome</u> • Lifestyle changes, particularly weight loss and physical exercise, are to be recommended to all individuals with the metabolic syndrome. These interventions improve not only BP, but the metabolic components of the syndrome and delay diabetes onset. • As the metabolic syndrome can be considered a 'pre-diabetic' state, antihypertensive agents potentially improving or at least not worsening insulin sensitivity, such as RAS blockers and calcium antagonists, should be considered as the preferred drugs. Beta-blockers (with the exception of vasodilating β-blockers) and diuretics should be considered only as additional drugs, preferably in association with a potassium-sparing agent. • It is recommended to prescribe antihypertensive drugs with particular care in hypertensive patients with metabolic disturbances when BP is ≥140/90 mmHg after a suitable period of lifestyle changes, and to maintain BP <140/90 mmHg. • BP lowering drugs are not recommended in individuals with metabolic syndrome and high normal BP. <u>Therapeutic strategies in hypertensive patients with nephropathy</u> • Lowering SBP to <140 mmHg should be considered. • When overt proteinuria is present, SBP values <130 mmHg may be considered, provided that changes in eGFR are monitored. • RAS blockers are more effective in reducing albuminuria than other antihypertensive agents, and are indicated in hypertensive patients in the presence of microalbuminuria or overt proteinuria. • Reaching BP goals usually requires combination therapy, and it is recommended to combine RAS blockers with other antihypertensive agents. • Combination of two RAS blockers, though potentially more effective in reducing proteinuria, is not recommended. • Aldosterone antagonists cannot be recommended in chronic kidney disease (CKD), especially in combination with a RAS blocker, because of the risk of excessive reduction in renal function and of hyperkalemia. <u>Therapeutic strategies in hypertensive patients with cerebrovascular disease</u> • It is not recommended to intervene with BP-lowering therapy during the first week after acute stroke irrespective of BP level, although clinical judgement should be used in the face of very high SBP values. • Antihypertensive treatment is recommended in hypertensive patients with a history of stroke or transient ischemic attack (TIA), even when initial SBP is in the 140 to 159 mmHg range. • In hypertensive patients with a history of stroke or TIA, a SBP goal of <140 mmHg should be considered. • In elderly hypertensives with previous stroke or TIA, SBP values for intervention and goal may be considered to be somewhat higher. • All drug regimens are recommended for stroke prevention, provided that BP is effectively reduced. <u>Therapeutic strategies in hypertensive patients with heart disease</u> • In hypertensive patients with CHD, a SBP goal <140 mmHg should be considered.

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	• In hypertensive patients with a recent myocardial infarction, β-blockers are recommended. In case of other CHD all antihypertensive agents can be used, but β-blockers and calcium antagonists are to be preferred for symptomatic reasons (angina). • Diuretics, β-blockers, ACE inhibitors, angiotensin receptor blockers, and/or mineralocorticoid receptor antagonists are recommended in patients with heart failure or severe left ventricular (LV) dysfunction to reduce mortality and hospitalization. • In patients with heart failure and preserved ejection fraction (EF), there is no evidence that antihypertensive therapy per se or any particular drug is beneficial. However, in these patients, as well as in patients with hypertension and systolic dysfunction, lowering SBP to around 140 mmHg should be considered. Treatment guided by relief of symptoms (congestion with diuretics, high heart rate with β-blockers, etc.) should also be considered. • ACE inhibitors and angiotensin receptor blockers (and β-blockers and mineralocorticoid receptor antagonists if heart failure coexists) should be considered as antihypertensive agents in patients at risk of new or recurrent atrial fibrillation. • It is recommended that all patients with left ventricular hypertrophy (LVH) receive antihypertensive agents. • In patients with LVH, initiation of treatment with one of the agents that have shown a greater ability to regress LVH should be considered, i.e. ACE inhibitors, angiotensin receptor blockers, and calcium antagonists. <u>Therapeutic strategies in hypertensive patients with atherosclerosis, arteriosclerosis, and peripheral artery disease (PAD)</u> • In the presence of carotid atherosclerosis, prescription of calcium antagonists and ACE inhibitors should be considered as these agents have shown a greater efficacy in delaying atherosclerosis progression than diuretics and β-blockers. • In hypertensive patients with a pulse wave velocity above 10 m/s, all antihypertensive drugs should be considered provided that a BP reduction to <140/90 mmHg is consistently achieved. • Antihypertensive therapy is recommended in hypertensive patients with PAD to achieve a goal of <140/90 mmHg, because of their high risk of myocardial infarction, stroke, heart failure, and CV death. ○ Though a careful follow up is necessary, β-blockers may be considered for the treatment of arterial hypertension in patients with PAD, since their use does not appear to be associated with exacerbation of PAD symptoms.
National Institute for Health and Clinical Excellence: **Hypertension in adults: diagnosis and management (2011)**[13] **Reaffirmed Nov 2016**	<u>Choosing antihypertensive drug treatment</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 people ≥80 years of age the same antihypertensive drug treatment as people aged 55 to 80 years, taking into account any comorbidities. • Offer antihypertensive drug treatment to women of child-bearing potential in line with the recommendations on Management of pregnancy with chronic hypertension and Breastfeeding in 'Hypertension in pregnancy' (NICE clinical guideline 107). <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

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	(ARB). 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 step one antihypertensive (ACE inhibitor, ARB) with a calcium channel blocker (CCB) to patients >55 years of age and to black patients of African or Caribbean family origin 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 chlorthalidone (12.5 to 25.0 mg once daily) or indapamide (1.5 mg modified-release once daily or 2.5 mg once daily) in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide.
	• For patients who are already receiving treatment with bendroflumethiazide or hydrochlorothiazide and whose blood pressure is stable and well controlled, continue treatment as is.
	• β-blockers are not a preferred initial therapy for hypertension; however, β-blockers may be considered in younger patients, particularly:
	  ○ Patients with an intolerance or contraindication to ACE inhibitors and ARBs.
	  ○ Women of child-bearing potential.
	  ○ People with evidence of increased sympathetic drive.
	• If treatment is initiated with a β-blocker and a second antihypertensive is required, add a CCB over a thiazide-like diuretic to reduce the risk of developing diabetes.
	
	<u>Step two treatment</u>
	• If blood pressure is not controlled with a step one antihypertensive, offer a step two treatment with a CCB in combination with an ACE inhibitor or an ARB.
	• If a CCB is not appropriate or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic.
	• For black patients of African or Caribbean family origin, consider an ARB in preference to an ACE inhibitor, in combination with a CCB.
	
	<u>Step three treatment</u>
	• Before considering step three treatment, review medication to ensure step two treatment is at optimal or best tolerated doses.
	• If three drugs are required to control blood pressure, the combination of an ACE inhibitor or ARB, CCB, and thiazide-like diuretic should be utilized.
	
	<u>Step four treatment</u>
	• Regard clinic blood pressure that remains >140/90 mmHg after treatment with the optimal or best tolerated doses of an ACE inhibitor or an ARB plus a CCB plus a diuretic as resistant hypertension, and consider adding a fourth antihypertensive drug and/or seeking expert advice.
	• For treatment of resistant hypertension at step four:
	  ○ Consider further diuretic therapy with low-dose spironolactone (25 mg once daily) if the blood potassium level is 4.5 mmol/l or lower. Use particular caution in people with a reduced estimated glomerular filtration rate because they have an increased risk of hyperkalemia.
	  ○ Consider higher-dose thiazide-like diuretic treatment if the blood potassium level is higher than 4.5 mmol/l.
	• If further diuretic therapy for resistant hypertension is not tolerated or is contraindicated or ineffective, consider an α-blocker or β-blocker.

International Society on Hypertension in	• To attain and maintain blood pressure (BP) below target levels, multiple antihypertensive drugs will be required in most hypertensive blacks.

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Blacks: **Management of High Blood Pressure in Blacks (2010)[14]**	• 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 (2012)[15]**	<u>Blood pressure management in chronic kidney disease (CKD) non-dialysis (ND) patients without diabetes mellitus</u> • The Work Group recommends that non-diabetic adults with CKD ND and urine albumin excretion <30 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >140 mm Hg systolic or >90 mm Hg diastolic be treated with blood pressure -lowering drugs to maintain a blood pressure that is consistently ≤140 mm Hg systolic and ≤90 mm Hg diastolic. • The Work Group suggests that non-diabetic adults with CKD ND and urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with BP-lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic. • The Work Group suggests that non-diabetic adults with CKD ND and urine albumin excretion >300 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with blood pressure -lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤ 80 mm Hg diastolic. • The Work Group suggests that an angiotensin receptor blocker (ARB) or angiotensin converting enzyme inhibitor (ACE-I) be used in non-diabetic adults with CKD ND and urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*) in whom treatment with blood pressure -lowering drugs is indicated. • The Work Group recommends that an ARB or ACE-I be used in non-diabetic adults with CKD ND and urine albumin excretion >300 mg per 24 hours (or equivalent*) in whom treatment with blood pressure -lowering drugs is indicated. <u>Blood pressure management in CKD ND patients with diabetes mellitus</u> • The Work Group recommends that adults with diabetes and CKD ND with urine albumin excretion <30 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >140 mm Hg systolic or >90 mm Hg diastolic be treated with BP-lowering drugs to maintain a blood pressure that is consistently ≤140 mm Hg systolic and ≤90 mm Hg diastolic. • The Work Group suggests that adults with diabetes and CKD ND with urine albumin excretion >30 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated

Clinical Guideline	Recommendations
	with BP-lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic. • The Work Group suggests that an ARB or ACE-I be used in adults with diabetes and CKD ND with urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*). • The Work Group recommends that an ARB or ACE-I be used in adults with diabetes and CKD ND with urine albumin excretion >300 mg per 24 hours (or equivalent*). <u>Blood pressure management in kidney transplant recipients (non–dialysis-dependent CKD of any stage with a kidney transplant [CKD T])</u> • The Work Group suggests that adult kidney transplant recipients whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic, irrespective of the level of urine albumin excretion. • In adult kidney transplant recipients, choose a blood pressure -lowering agent after taking into account the time after transplantation, use of calcineurin inhibitors, presence or absence of persistent albuminuria, and other co morbid conditions. <u>Blood pressure management in children with CKD ND</u> • The Work Group recommends that in children with CKD ND, blood pressure -lowering treatment is started when blood pressure is consistently above the 90th percentile for age, sex, and height. • The Work Group suggests that in children with CKD ND (particularly those with proteinuria), blood pressure is lowered to consistently achieve systolic and diastolic readings less than or equal to the 50th percentile for age, sex, and height, unless achieving these targets is limited by signs or symptoms of hypotension. • The Work Group suggests that an ARB or ACE-I be used in children with CKD ND in whom treatment with blood pressure -lowering drugs is indicated, irrespective of the level of proteinuria. <u>Blood pressure management in elderly persons with CKD ND</u> • Tailor blood pressure treatment regimens in elderly patients with CKD ND by carefully considering age, co-morbidities and other therapies, with gradual escalation of treatment and close attention to adverse events related to blood pressure treatment, including electrolyte disorders, acute deterioration in kidney function, orthostatic hypotension and drug side effects. *Approximate equivalents for albumin excretion rate per 24 hours is expressed as protein excretion rate per 24 hours, albumin/creatinine ratio, protein/creatinine ratio, and protein reagent strip results.
American Diabetes Association: **Standards of Medical Care in Diabetes (2017)**[16]	<u>Hypertension/blood pressure control</u> • Blood pressure should be measured at every routine visit. Patients found to have elevated blood pressure should have blood pressure confirmed on a separate day. • Most patients with diabetes and hypertension should be treated to a systolic blood pressure goal of <140 mmHg and a diastolic blood pressure goal of <90 mmHg. • Lower systolic and diastolic blood pressure targets, such as 130/80 mmHg, may be appropriate for individuals at high risk of cardiovascular disease, if they can be achieved without undue treatment burden. • In pregnant patients with diabetes and chronic hypertension, blood pressure targets of 120 to 160/80 to 105 mmHg are suggested in the interest of optimizing long-term maternal health and minimizing impaired fetal growth. • Patients with confirmed office-based blood pressure >140/90 mmHg should, in

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	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). 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. • For patients with blood pressure >120/80 mmHg, lifestyle intervention consists of weight loss if overweight or obese; a Dietary Approaches to Stop Hypertension–style dietary pattern including reducing sodium and increasing potassium intake; moderation of alcohol intake; and increased physical activity. <u>Coronary heart disease</u> • In asymptomatic patients, routine screening for coronary artery disease is not recommended as it does not improve outcomes as long as atherosclerotic cardiovascular disease risk factors are treated. • Consider investigations for coronary artery disease in the presence of any of the following: atypical cardiac symptoms (e.g., unexplained dyspnea, chest discomfort); signs or symptoms of associated vascular disease including carotid bruits, transient ischemic attack, stroke, claudication, or peripheral arterial disease; or electrocardiogram abnormalities (e.g., Q waves). • In patients with known atherosclerotic cardiovascular disease, use aspirin and statin therapy (if not contraindicated) and consider ACE inhibitor therapy to reduce the risk of cardiovascular events. • In patients with prior myocardial infarction, β-blockers should be continued for at least two years after the event. • In patients with symptomatic heart failure, thiazolidinedione treatment should not be used. • In patients with type 2 diabetes with stable congestive heart failure, metformin may be used if estimated glomerular filtration remains >30 mL/min but should be avoided in unstable or hospitalized patients with congestive heart failure. <u>Diabetic 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, in all patients with type 2 diabetes, and in all patients with comorbid hypertension. • Optimize glucose control to reduce the risk or slow the progression of diabetic kidney disease. • Optimize blood pressure control to reduce the risk or slow the progression of diabetic kidney disease. • For people with nondialysis-dependent diabetic kidney disease, dietary protein

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	intake should be approximately 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. • 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) B 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 or changes in potassium when ACE inhibitors, angiotensin receptor blockers, or diuretics are used. • Continued monitoring of urinary albumin–to–creatinine ratio in patients with albuminuria treated with an ACE inhibitor or an angiotensin receptor blocker is reasonable to assess the response to treatment and progression of diabetic kidney disease. • An ACE inhibitor or an angiotensin receptor blocker is not recommended for the primary prevention of diabetic kidney disease 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. • When estimated glomerular filtration rate is <60 mL/min/1.73 m^2, evaluate and manage potential complications of chronic kidney disease. • Patients should be referred for evaluation for renal replacement treatment if they have an estimated glomerular filtration rate <30 mL/min/1.73 m^2. • Promptly refer to a physician experienced in the care of kidney disease 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)
Single Entity Agents					
Aliskiren	2.5	47 to 51	Liver, minor (% not reported)	Feces (91) Renal (<1)	40
Combination Products					

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
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[4]

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		

Adverse Events	Single Entity Agents	Combination Products
	Aliskiren	Aliskiren and HCTZ
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
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

Adverse Events	Single Entity Agents	Combination Products
	Aliskiren	Aliskiren and HCTZ
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	Safety and efficacy in children have not been established.	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.[17] (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.[18] (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.[19] (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.[20] (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.[21] (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.[22] (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.[23] (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.[24] (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.[25] (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.[26] (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.[27] (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.[28] (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.[29] (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.[30] (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.[31] (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.[32] (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.[33] (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.[34] (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.[35] (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.[36] (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.[37] (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.[38] (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.[39] (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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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.[40] (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.[41] (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:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			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.[42] (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.[43] (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.[44] (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.[45] (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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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.[46] (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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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.[47] (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:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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.[48] (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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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.[49] (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

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).
Dietz et al.[50] (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.[51] (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.[52] (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.[53] (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.[54] (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.[55] (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.[56] (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.[57] (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®	$$$$$	N/A
Combination Products				
Aliskiren and HCTZ	tablet	Tekturna HCT®	$$$$	N/A

*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. There are no generic renin inhibitor products currently available; however, hydrochlorothiazide is available generically.

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 renin inhibitors, with the exception of European Society of Hypertension and European Society of Cardiology which state that evidence is available to justify the use of aliskiren for the management of hypertension, particularly in combination with other antihypertensive agents.[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).[9] Several guidelines consistently recommend that the selection of an antihypertensive agent be based on compelling indications for use.[9-16] Most patients will require more than one antihypertensive medication to achieve blood pressure goals.[9-16]

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.[19-57] Most patients will require more than one antihypertensive medication to achieved blood pressure goals.[9-16] 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.[6-8,17] 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.[54-57] 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
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Pharmacotherapy Review of Loop Diuretics
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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.[3-6] 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 August 2015.

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®*	none
Furosemide	injection, solution, tablet	Lasix®*	furosemide
Torsemide	tablet	Demadex®*	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 College of Cardiology/American Heart Association: **Guideline for the Management of Heart Failure (2013)[10]**	<u>Treatment of Stage A heart failure (HF)</u> • Hypertension and lipid disorders should be controlled in accordance with guidelines to lower the risk of HF. (Level of Evidence (LoE): A) • Other conditions that may lead to or contribute to HF, such as obesity, diabetes mellitus, tobacco use, and known cardiotoxic agents, should be controlled or avoided. (LoE: C) <u>Treatment of Stage B heart failure</u>

Clinical Guideline	Recommendation(s)
	• In patients with a history of MI and reduced EF, ACE inhibitors or ARBs should be used to prevent HF. (LoE: A) • In patients with MI and reduced EF, evidence-based β-blockers (using one of three proven to reduce mortality [i.e., bisoprolol, carvedilol, and sustained-release metoprolol succinate]) should be used to prevent HF. (LoE: B) • In patients with MI, statins should be used to prevent HF. (LoE: A) • ACE inhibitors and β-blockers should be used in all patients with a reduced EF to prevent symptomatic HF, even if they do not have a history of MI. (LoE: A and C, respectively) • Blood pressure should be controlled to prevent symptomatic HF. (LoE: A) • Nondihydropyridine calcium channel blockers may be harmful in patients with low LVEF. (LoE: C) <u>Pharmacological treatment for Stage C HFrEF</u> • Recommendations for patients in Stages A and B are recommended where appropriate for patients in Stage C. (LoE: A, B, and C as appropriate) • Diuretics are recommended in patients with HFrEF who have evidence of fluid retention, unless contraindicated, to improve symptoms. (LoE: C) • ACE inhibitors are recommended in patients with HFrEF and current or prior symptoms, unless contraindicated, to reduce morbidity and mortality. ARBs are recommended as alternative therapy in ACE inhibitor intolerant patients. (LoE: A) • Use of one of the three β-blockers proven to reduce mortality is recommended for all patients with current or prior symptoms of HFrEF, unless contraindicated, to reduce morbidity and mortality. (LoE: A) • Aldosterone receptor antagonists are recommended in patients with NYHA class II–IV HF and who have LVEF of ≤35%, unless contraindicated, to reduce morbidity and mortality. Patients with NYHA class II HF should have a history of prior cardiovascular hospitalization or elevated plasma natriuretic peptide levels to be considered for aldosterone receptor antagonists. Creatinine should be ≤2.5 mg/dL in men or ≤2.0 mg/dL in women (or estimated glomerular filtration rate >30 mL/min/1.73 m^2), and potassium should be <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) • The combination of hydralazine and isosorbide dinitrate is recommended to reduce morbidity and mortality for patients self-described as African Americans with NYHA class III–IV HFrEF receiving optimal therapy with ACE inhibitors and β-blockers, unless contraindicated. (LoE: A) • Digoxin can be beneficial in patients with HFrEF, unless contraindicated, to decrease hospitalizations for HF. (LoE: B) • Patients with chronic HF with permanent/persistent/paroxysmal AF and an additional risk factor for cardioembolic stroke (history of hypertension, diabetes mellitus, previous stroke or transient ischemic attack, or ≥75 years of age) should receive chronic anticoagulant therapy. (LoE: A) • Statins are not beneficial as adjunctive therapy when prescribed solely for the diagnosis of HF in the absence of other indications for their use. (LoE: A) • Calcium channel blockers are not recommended as routine treatment for patients with HFrEF. (LoE: A) <u>Pharmacological treatment for Stage C HFpEF</u> • Blood pressure should be controlled according to published clinical practice guidelines. (LoE: B) • Diuretics should be used for relief of symptoms due to volume overload. (LoE:

Clinical Guideline	Recommendation(s)
	C) • The use of β-blocking agents, ACE inhibitors, and ARBs in patients with hypertension is reasonable to control blood pressure in patients with HFpEF. (LoE: C) <u>Treatment of Stage D (advanced/refractory) HF</u> • Fluid restriction (1.5 to 2 L/d) is reasonable, especially in patients with hyponatremia, to reduce congestive symptoms. (LoE: C) • Until definitive therapy (e.g., coronary revascularization, mechanical circulatory support, heart transplantation) or resolution of the acute precipitating problem, patients with cardiogenic shock should receive temporary intravenous inotropic support to maintain systemic perfusion and preserve end-organ performance. (LoE: C) • Continuous intravenous inotropic support is reasonable as "bridge therapy" in patients with stage D HF refractory to medical therapy and device therapy who are eligible for and awaiting mechanical circulatory support or cardiac transplantation. (LoE: B) • Long-term use of either continuous or intermittent, intravenous parenteral positive inotropic agents, in the absence of specific indications or for reasons other than palliative care, is potentially harmful in the patient with HF. (LoE: B)
Heart Failure Society of America: **Heart Failure Society of America 2010 Comprehensive Heart Failure Practice Guidelines (Executive Summary) (2010)[11]**	<u>Patients with left ventricular systolic dysfunction</u> • ACE inhibitors should be used in all patients with a LVEF ≤40%, unless otherwise contraindicated. • ARBs may be used in patients who are intolerant to ACE inhibitors. Hydralazine and a nitrate may be used in patients intolerant to ACE inhibitors and ARBs, or in whom such therapy is contraindicated. • The combination of an ACE inhibitor and a β-blocker is recommended in all patients with a LVEF ≤40%. • The routine use of an ARB with a combination of an ACE inhibitor and β-blocker in patients who have had a MI and have left ventricular dysfunction is not recommended. • The addition of an ARB can be considered in patients with heart failure due to reduced LVEF who have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor and a β-blocker. • Individual ARBs may be considered as initial therapy (instead of an ACE inhibitor) in patients with heart failure who have had a MI and in patients with chronic heart failure and systolic dysfunction. • ARBs are recommended in patients who cannot tolerate ACE inhibitors due to cough. The combination of hydralazine and an oral nitrate may be considered in such patients not tolerating ARB therapy. • Patients intolerant to ACE inhibitors from hyperkalemia or renal insufficiency are likely to experience the same side effects with ARBs. In these cases, the combination of hydralazine and an oral nitrate should be considered. • ARBs should be considered in patients experiencing angioedema while on ACE inhibitors based on their underlying risk and with recognition that angioedema has been reported infrequently with ARBs. The combination of hydralazine and oral nitrates may be considered in such patients not tolerating ARB therapy. • A combination of hydralazine and an oral nitrate is recommended in African American patients with heart failure and reduced left ventricular ejection fraction (LVEF) who are on a standard regimen of an ACE inhibitor (or ARB) and a β-blocker. • A combination of hydralazine and an oral nitrate may be considered in non–African American patients with heart failure and reduced LVEF who are symptomatic despite optimization of standard therapy. • Administration of an aldosterone antagonist is recommended for patients with

Clinical Guideline	Recommendation(s)
	New York Heart Association (NYHA) class IV (or class III, previously class IV) heart failure from reduced LVEF (<35%) while receiving standard therapy, including diuretics. • Administration of an aldosterone antagonist should be considered in patients following an acute MI, with clinical heart failure signs and symptoms or history of diabetes mellitus, and an LVEF <40%. Patients should be on standard therapy, including an ACE inhibitor (or ARB) and a β-blocker. • The triple combination of an ACE inhibitor, an ARB, and an aldosterone antagonist is not recommended because of the high risk of hyperkalemia. <u>Patients with hypertension and symptomatic left ventricular dysfunction with left ventricular dilation and low LVEF</u> • ACE inhibitors, ARBs, β-blockers, aldosterone inhibitors, and isosorbide dinitrate/hydralazine in various combinations (with a loop diuretic if needed) are recommended. • If blood pressure remains >130/80 mm Hg, a dihydropyridine calcium channel blocker (e.g., amlodipine or felodipine) may be considered or other antihypertensive medication doses increased. <u>Managing heart failure in special populations</u> • The combination of hydralazine/isosorbide dinitrate is recommended for African American women with moderate to severe heart failure symptoms who are on background neurohormonal inhibition. • A combination of hydralazine and isosorbide dinitrate is recommended as part of standard therapy in addition to β-blockers and ACE-inhibitors for African Americans with left ventricular systolic dysfunction and NYHA class II-IV heart failure. • As in all patients, but especially in the elderly, careful attention to volume status, the possibility of symptomatic cerebrovascular disease and the presence of postural hypotension are recommended during therapy with ACE inhibitors, β-blockers and diuretics. <u>Patients with heart failure and preserved LVEF</u> • ACE inhibitors or ARBs should be considered in this patient population. • ACE inhibitors should be considered in patients with heart failure and symptomatic atherosclerotic cardiovascular disease or diabetes and at least one other risk factor. ARBs may be used in patients who are intolerant to ACE inhibitors. • Beta-blocker treatment is recommended in patients with HF and preserved LVEF who have prior MI, hypertension, or AF. • Calcium channel blockers should be considered in patients with heart failure and preserved LVEF who have atrial fibrillation requiring ventricular rate control and intolerance to β-blockers (consider diltiazem or verapamil), symptom-limiting angina, or hypertension. • Diuretic therapy is recommended in all patients with heart failure and clinical evidence of volume overload, including those with preserved LVEF. • Treatment may begin with either a thiazide or loop diuretic. In more severe volume overload or if response to a thiazide is inadequate, treatment with a loop diuretic should be implemented. • Excessive diuresis, which may lead to orthostatic changes in blood pressure and worsening renal function, should be avoided. <u>Patients with heart failure and CAD</u> • Calcium channel blockers should be considered in patients who have angina despite optimization of β-blocker and nitrates. Amlodipine and felodipine are

Clinical Guideline	Recommendation(s)
	preferred in patients with decreased systolic function. <u>Patients with heart failure and hypertension</u> • Patients with left ventricular hypertrophy or left ventricular dysfunction without left ventricular dilation should be treated to a goal blood pressure of <130/80 mm Hg. Treatment with several drugs may be necessary, including an ACE inhibitor (or ARB), a diuretic and a β-blocker or calcium channel blocker. • Patients with asymptomatic left ventricular dysfunction and left ventricular dilation and a reduced ejection fraction should receive an ACE inhibitor and a β-blocker. If blood pressure remains elevated (>130/80 mm Hg), the addition of a diuretic is recommended, followed by a calcium channel blocker or other antihypertensive agent. • If blood pressure remains >130/80 mm Hg, then the addition of a thiazide diuretic is recommended, followed by a dihydropyridine calcium channel blocker (e.g., amlodipine or felodipine) or other antihypertensive drugs. <u>Patients at risk for development of heart failure</u> • ACE inhibitors are recommended in patients who are at risk for the development of heart failure including patients with CAD, peripheral vascular disease, stroke, diabetes and another major risk factor, and patients with diabetes who smoke and have microalbuminuria. <u>Patients with asymptomatic heart failure and reduced LVEF</u> • ACE inhibitors are recommended in asymptomatic patients with reduced LVEF (<40%). • ARBs may be used in patients who are intolerant to ACE inhibitors. • Routine use of a combination of ACE inhibitors and ARBs is not recommended. • β-blocker therapy should be considered. <u>Patients with heart failure and ischemic heart disease</u> • ACE inhibitor therapy is recommended in all patients with either reduced or preserved LVEF after a MI. • Beta-blockers are recommended for the management of all patients with reduced LVEF or post-MI. • ACE inhibitor and β-blocker therapy should be initiated early (<48 hours) during hospitalization in hemodynamically stable patients who are post-MI with reduced LVEF or heart failure. • Calcium channel blockers may be considered in patients with HF who have angina despite the optimal use of β-blockers and nitrates. <u>Managing heart failure in the elderly, women and African Americans</u> • Standard regimens of ACE inhibitors and β-blockers are recommended in elderly patients with heart failure. • ACE inhibitor and β-blocker therapy are recommended in all women with heart failure and left ventricular systolic dysfunction. • ACE inhibitor and β-blocker therapy are recommended in all African American patients with heart failure and left ventricular systolic dysfunction. ARBs may be substituted in patients who are intolerant to ACE inhibitors. <u>Heart failure in patients with reduced ejection fraction</u> • ACE inhibitors are recommended in asymptomatic patients with reduced LVEF (<40%). • ARBs may be used in patients who are intolerant to ACE inhibitors. • β-blockers shown to be effective in clinical trials of patients with heart failure are

Clinical Guideline	Recommendation(s)
	recommended for patients with a LVEF ≤40%. • The combination of a β-blocker and an ACE inhibitor is recommended as routine therapy for asymptomatic patients with a LVEF ≤40%. The evidence is stronger in patients with a history of MI. • β-blocker therapy is recommended for patients with a recent decompensation of heart failure after optimization of volume status and successful discontinuation of intravenous diuretics and vasoactive drugs. Whenever possible, β-blocker therapy should be initiated in the hospital setting at a low dose prior to discharge of stable patients. • β-blocker therapy is recommended in the great majority of patients with heart failure and reduced LVEF, even if there is concurrent diabetes, chronic obstructive pulmonary disease or peripheral vascular disease. Caution may be warranted in these patients. • It is recommended that β blockade be initiated at low doses and uptitrated gradually. • It is recommended that β-blocker therapy be continued in most patients experiencing a symptomatic exacerbation of heart failure during chronic maintenance treatment, unless they develop cardiogenic shock, refractory volume overload or symptomatic bradycardia. • The routine use of an ARB is not recommended in addition to an ACE inhibitor and a β-blocker in patients with a recent acute MI and reduced LVEF. • The addition of an ARB should be considered in patients with heart failure due to reduced LVEF who have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor and a β-blocker. • Administration of an aldosterone antagonist is recommended for patients with NYHA class IV (or class III, previously class IV) HF from reduced LVEF (<35%) while receiving standard therapy, including diuretics. • Diuretic therapy is recommended to restore and maintain normal volume status in patients with clinical evidence of fluid overload, generally manifested by congestive symptoms or signs of elevated filling pressures. Loop diuretics rather than thiazide-type diuretics are typically necessary to restore normal volume status in patients with heart failure. • The initial dose of diuretic may be increased as necessary to relieve congestion, and restoration of normal volume status may require multiple adjustments, especially in patients with severe fluid overload evidenced by massive edema or ascites. After a diuretic effect is achieved with loop diuretics (short acting), increasing administration frequency to twice or even three times/day will provide more diuresis with less physiologic perturbation than larger single doses. • Oral torsemide may be considered in patients in whom poor absorption of oral medication or erratic diuretic effect may be present. Particularly in patients with right-sided heart failure and refractory fluid retention despite high doses of other loop diuretics. • Intravenous administration of diuretics may be necessary to relieve congestion. • Diuretic refractoriness may represent patient nonadherence, a direct effect of diuretic use on the kidney or progression of underlying cardiac dysfunction. • Addition of chlorothiazide or metolazone, once or twice daily, to loop diuretics should be considered in patients with persistent fluid retention despite high dose loop diuretic therapy. Chronic daily use should be avoided if possible because of the potential for electrolyte shifts and volume depletion. These drugs may be used periodically (every other day or weekly) to optimize fluid management. Metolazone will generally be more potent and much longer acting in this setting and in patients with chronic renal insufficiency, so administration should be adjusted accordingly. Volume status and electrolytes must be monitored closely when multiple diuretics are used. • Careful observation for the development of side effects is recommended in

Clinical Guideline	Recommendation(s)

	patients treated with diuretics, especially when high doses or combination therapy are used. Patients should undergo routine laboratory studies and clinical examination as dictated by their clinical response.
	• Patients requiring diuretic therapy to treated fluid retention associated with heart failure generally require chronic treatment, although often at lower doses than those required initially to achieve diuresis. Decreasing or discontinuing therapy may be considered in patients experiencing significant improvement in clinical status and cardiac function or in those who successfully restrict dietary sodium intake. These patients may undergo cautious weaning of diuretic dose and frequency with careful observation for recurrent fluid retention.
	• Patients and caregivers should be given education on the early signs of fluid retention and the plan for initial therapy.
	• Selected patients may be educated to adjust daily dose of diuretic in response to weight gain from fluid overload.
	
	<u>Evaluation and management of patients with acute decompensated heart failure</u>
	• Patients admitted with acute decompensated heart failure and evidence of fluid overload be treated initially with loop diuretics; usually given intravenously rather than orally. Ultrafiltration may be considered in lieu of diuretics.
	• Diuretics should be administered at doses needed to produce a rate of diuresis sufficient to achieve optimal volume status with relief of signs and symptoms of congestion, without inducing an excessively rapid reduction in intravascular volume or serum electrolytes.
	• Monitoring of daily weights, intake and output is recommended to assess clinical efficacy of diuretic therapy.
	• Careful observation for development of a variety of side effects, including renal dysfunction, electrolyte abnormalities, symptomatic hypotension and gout is recommended in patients treated with diuretics, especially when high doses or combination therapy is used.
	• Careful observation for the development of renal dysfunction is recommended in patients treated with diuretics. Patients with moderate to severe renal dysfunction and evidence of fluid retention should continue to be treated with diuretics. In the presence of severe fluid overload, renal dysfunction may improve with diuresis.
	• When congestion fails to improve in response to diuretic therapy, the following options should be considered:
	  ○ Re-evaluating the presence/absence of congestion.
	  ○ Sodium and fluid restriction.
	  ○ Increasing doses of loop diuretic.
	  ○ Continuous infusion of a loop diuretic.
	  ○ Addition of a second type of diuretic orally (metolazone or spironolactone) or intravenously (chlorothiazide).
	  ○ Ultrafiltration may be considered as well.

European Society of Cardiology: **Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (2016)**[12]	<u>Pharmacological treatments indicated in patients with symptomatic (NYHA Class II-IV) heart failure with reduced ejection fraction</u> • An ACE inhibitor is recommended, in addition to a beat-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death. • A mineralocorticoid receptor antagonist 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. • Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion. • 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. • 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. • 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 heart failure with preserved ejection fraction and heart failure with mid-range ejection fraction</u> • It is recommended to screen patients with HFpEF or HFmrEF (mid-range) 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 or HFmrEF in order to alleviate symptoms and signs. <u>Recommendations for initial management of a rapid ventricular rate in patients with heart failure and atrial fibrillation in the acute or chronic setting</u> • Urgent electrical cardioversion is recommended if AF is thought to be contributing to the patient's hemodynamic compromise in order to improve the patient clinical condition. • For patients in NYHA Class IV, in addition to treatment for acute HF, an intravenous bolus of amiodarone or, in digoxin-naïve patients, an intravenous bolus of digoxin should be considered to reduce the ventricular rate. • For patients in NYHA Class I–III, a β-blocker, usually given orally, is safe and therefore is recommended as first-line treatment to control ventricular rate, provided the patient is euvolemic. • For patients in NYHA Class I–III, digoxin should be considered when ventricular rate remains high despite β-blockers or when β-blockers are not tolerated or contraindicated. • Treatment with dronedarone to improve ventricular rate control is not

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	recommended due to safety concerns. Recommendations for cardiac imaging in patients with suspected or established heart failure • Transthoracic Echocardiogram (TTE) is recommended for the assessment of myocardial structure and function in subjects with suspected HF in order to establish a diagnosis of HFrEF, HFmrEF, or HFpEF. • TTE is recommended for the assessment of LVEF in order to identify patients with HF who would be suitable for evidence-based pharmacological and device treatment recommended for HFrEF. Recommendations aiming to prevent or delay the development of overt heart failure or prevent death before the onset of symptoms • Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life. • ACE inhibitor is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction in order to prevent or delay the onset of HF and prolong life. • Beta-blocker is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction, in order to prevent or delay the onset of HF and prolong life. Pharmacological treatments indicated in patients with symptomatic 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 β-blocker is recommended, in addition to an ACE inhibitor, for patients with stable, symptomatic HFrEF to reduce the risk of HF hospitalization and death. • A mineralocorticoid receptor antagonist 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. Other pharmacological treatments recommended in selected patients with symptomatic heart failure with reduced ejection fraction • Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion. • 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. Treatments (or combinations of treatments) that may cause harm in patients with symptomatic (New York Heart Association Class II–IV) heart failure with reduced ejection fraction • Diltiazem or verapamil are not recommended in patients with HFrEF, as they increase the risk of HF worsening and HF hospitalization. • The addition of an ARB (or a renin inhibitor) to the combination of an ACE inhibitor and a mineralocorticoid receptor antagonist is not recommended in patients with HF, because of the increased risk of renal dysfunction and hyperkalemia. Not-recommended treatments of co-morbidities in patients with heart failure • Thiazolidinediones (glitazones) are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization. • NSAIDs or COX-2 inhibitors are not recommended in patients with HF, as they

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	increase the risk of HF worsening and HF hospitalization. Recommendations for the 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. • In patients with new-onset AHF or those with chronic, decompensated HF not receiving oral diuretics the initial recommended dose should be 20 to 40 mg intravenous furosemide (or equivalent); for those on chronic diuretic therapy, initial intravenous dose should be at least equivalent to oral dose. • It is recommended to give diuretics either as intermittent boluses or a continuous infusion, and the dose and duration should be adjusted according to the patients' symptoms and clinical status. • Inotropic agents are not recommended unless the patient is symptomatically hypotensive or hypoperfused because of safety concern.
Eighth Joint National Committee (JNC 8): **2014 Evidence-based Guideline for the Management of High Blood Pressure in Adults (2014)**[13]	• 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

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	a hypertension specialist may be indicated.
American Society of Hypertension/ International Society of Hypertension: **Clinical Practice Guidelines for the Management of Hypertension in the Community (2014)**[14]	Nonpharmacologic treatment • In patients with hypertension that is no more severe than stage one and is not associated with evidence of abnormal cardiovascular findings or other cardiovascular risks, six to 12 months of lifestyle changes can be attempted in the hope that they may be sufficiently effective to make it unnecessary to use medicines. • It may be prudent to start treatment with drugs sooner if it is clear that the blood pressure is not responding to the lifestyle methods or if other risk factors appear. • Weight loss: In patients who are overweight or obese, weight loss is helpful in treating hypertension, diabetes, and lipid disorders. • Salt reduction: Reduction of salt intake is recommended because it can reduce blood pressure and decrease the need for medications in patients who are "salt sensitive." • Exercise: Regular aerobic exercise can help reduce blood pressure. • Alcohol consumption: Up to two drinks a day can be helpful in protecting against cardiovascular events, but greater amounts of alcohol can raise blood pressure and should therefore be discouraged. In women, alcohol should be limited to one drink a day. • Cigarette smoking: Stopping smoking will not reduce blood pressure, but since smoking by itself is such a major cardiovascular risk factor, patients must be strongly urged to discontinue this habit. Drug treatment of hypertension • Treatment with drugs should be started in patients with blood pressures >140/90 mm Hg in whom lifestyle treatments have not been effective. • In patients with stage two hypertension (blood pressure ≥160/100 mm Hg), drug treatment should be started immediately after diagnosis, usually with a two-drug combination, without waiting to see the effects of lifestyle changes. • For patients older than 80 years, the suggested threshold for starting treatment is at levels ≥150/90 mm Hg. Thus, the target of treatment should be <140/90 mm Hg for most patients but <150/90 mm Hg for older patients (unless these patients have chronic kidney disease or diabetes, when <140/90 mm Hg can be considered). • Most patients will require more than one drug to achieve control of their blood pressure. • In general, increase the dose of drugs or add new drugs at approximately two to three week intervals. This frequency can be faster or slower depending on the judgment of the practitioner. In general, the initial doses of drugs chosen should be at least half of the maximum dose so that only one dose adjustment is required thereafter. It is generally anticipated that most patients should reach an effective treatment regimen, whether one, two, or three drugs, within six to eight weeks. • Choice of drugs should be influenced by the age, ethnicity/race, and other clinical characteristics of the patient. • The choice of drugs will also be influenced by other conditions (e.g., diabetes and coronary disease) associated with the hypertension. Pregnancy also influences drug choice. • Long-acting drugs that need to be taken only once daily are preferred to shorter-acting drugs that require multiple doses because patients are more likely to follow a simple treatment regimen. • This guideline only makes recommendations for drug classes, not individual agents. There is an assumption, unless otherwise stated, that all drugs in a class are similar to each other. • Drug selectin when hypertension is the only or main concern: ○ For black patients of all ages, use calcium channel blocker (CCB) or thiazide

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	diuretic as first drug, then add angiotensin receptor blocker (ARB) or angiotensin-converting enzyme (ACE) inhibitor if needed. ○ For white and other non-black patients <60 years of age, use ARB or ACE inhibitor as first drug, then add CCB or thiazide diuretic if needed. ○ For white and other non-black patients ≥60 years of age, use CCB or thiazide diuretic as first drug, then add ARB or ACE inhibitor if needed. • Drug selection when hypertension is associated with other conditions: ○ For patients with hypertension and diabetes, use ARB or ACE inhibitor as first drug (note, in black patients it is acceptable to start with a CCB or thiazide), then add CCB or thiazide diuretic (unless starting on CCB or thiazide in black patients) if needed. ○ For patients with hypertension and chronic kidney disease, use ARB or ACE inhibitor as first drug, then add CCB or thiazide diuretic if needed. ○ For patients with hypertension and clinical coronary artery disease, use β-blocker plus ARB or ACE inhibitor as first drugs, then add CCB or thiazide diuretic if needed. ○ For patients with hypertension and stroke history, use ACE inhibitor or ARB as first drug, then add thiazide diuretic or CCB if needed. • For patients with hypertension and heart failure, patients with h symptomatic heart failure should usually receive an ARB or ACE inhibitor plus β-blocker plus diuretic plus spironolactone regardless of blood pressure. A dihydropyridine CCB can be added if needed for blood pressure control.
Hypertension Canada: **2017 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults (2017)**[15]	<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. <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

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	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>Guidelines for individuals 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> • 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

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	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.
	
	Treatment of hypertension in association with stroke
	• BP management in acute ischemic stroke (onset to 72 hours)
	  ○ For patients with ischemic stroke not eligible for thrombolytic therapy, treatment of hypertension in the setting of acute ischemic stroke or transient ischemic attack should not be routinely undertaken. Extreme BP increases (e.g., SBP >220 mmHg or DBP >120 mmHg) may be treated to reduce the BP by approximately 15%, and not more than 25%, over the first 24 hours with gradual reduction thereafter. Avoid excessive lowering of BP because this might exacerbate existing ischemia or might induce ischemia, particularly in the setting of intracranial arterial occlusion or extracranial carotid or vertebral artery occlusion. Pharmacological agents and routes of administration should be chosen to avoid precipitous decreases in BP.
	  ○ For patients with ischemic stroke eligible for thrombolytic therapy, very high BP (>185/110 mmHg) should be treated concurrently in patients receiving thrombolytic therapy for acute ischemic stroke to reduce the risk of secondary intracranial hemorrhage.
	• 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)
	  ○ For patients with intracerebral hemorrhage (ICH) in the hyperacute phase (in the first 24 hours) SBP lowering to <140 mmHg should be avoided because of an absence of benefit (relative to a target of <180 mmHg) and some suggestion of harm.
	
	Treatment of hypertension in association with LVH

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	• 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> • For patients with nondiabetic chronic kidney disease, target BP is <140/90 mmHg. • For patients with hypertension and proteinuric chronic kidney disease (urinary protein >500 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. • Thiazide/thiazide-like diuretics are recommended as additive antihypertensive therapy. For patients with chronic kidney disease and volume overload, loop diuretics are an alternative. • 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. • In patients with hypertension attributable to FMD-related renal artery stenosis, revascularization should be considered. • 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 2 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. Combination therapy using two first-line agents may also be considered as initial treatment of hypertension if SBP is 20 mmHg greater than target or if DBP is 10 mmHg greater than target. However, caution should be exercised in patients in whom a substantial decrease in BP is more likely or poorly tolerated (e.g., elderly patients and patients with autonomic neuropathy). • 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

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	therapy with an ACE inhibitor is being considered, a dihydropyridine CCB is preferable to a thiazide/thiazide-like diuretic.
European Society of Hypertension/ European Society of Cardiology: **2013 Guidelines for the management of arterial hypertension (2013)**[16]	The 2013 guidelines on hypertension of the European Society of Hypertension and the European Society of Cardiology follow the guidelines jointly issued by the two societies in 2003 and 2007. <u>Treatment strategies and choice of antihypertensive drugs</u> • Diuretics (including thiazides, chlorthalidone, and indapamide), β-blockers, calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) are all suitable for the initiation and maintenance of antihypertensive treatment, either as monotherapy or in some combinations. • Some agents should be considered as the preferential choice in specific conditions because used in trials in those conditions or because of greater effectiveness in specific types of organ damage. • Initiation of antihypertensive therapy with a two-drug combination may be considered in patients with markedly high baseline blood pressure (BP) or at high cardiovascular (CV) risk. • The combination of two antagonists of the renin-angiotensin system (RAS) is not recommended and should be discouraged. • Other drug combinations should be considered and probably are beneficial in proportion to the extent of BP reduction. However, combinations that have been successfully used in trials may be preferable. • Combinations of two antihypertensive drugs at fixed doses in a single tablet may be recommended and favored, because reducing the number of daily pills improves adherence, which is low in patients with hypertension. <u>Treatment strategies in white-coat and masked hypertension</u> • In white-coat hypertensives without additional risk factors, therapeutic intervention may be limited to lifestyle changes only, but this decision should be accompanied by close follow-up. • In white-coat hypertensives with a higher CV risk because of metabolic derangements or asymptomatic organ damage, drug treatment may be considered in addition to lifestyle changes. • In masked hypertension, both lifestyle measures and antihypertensive drug treatment should be considered, because this type of hypertension has been consistently found to have a CV risk very close to that of in- and out-of-office hypertension. <u>Antihypertensive treatment strategies in the elderly</u> • In elderly hypertensives with SBP ≥160 mmHg there is solid evidence to recommend reducing SBP to between 150 and 140 mmHg. • In fit elderly patients <80 years old antihypertensive treatment may be considered at SBP values ≥140 mmHg with a target SBP <140 mmHg if treatment is well tolerated. • In individuals older than 80 years with an initial SBP ≥160 mmHg, it is recommended to reduce SBP to between 150 and 140 mmHg, provided they are in good physical and mental conditions. • In frail elderly patients, it is recommended to leave decisions on antihypertensive therapy to the treating physician, and based on monitoring of the clinical effects of treatment. • Continuation of well-tolerated antihypertensive treatment should be considered when a treated individual becomes an octogenarian. • All hypertensive agents are recommended and can be used in the elderly, although diuretics and calcium antagonists may be preferred in isolated systolic

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	hypertension. <u>Treatment strategies in hypertensive women</u> • Hormone therapy and selective estrogen receptor modulators are not recommended and should not be used for primary or secondary prevention of CVD. • If treatment of younger perimenopausal women is considered for severe menopausal symptoms, the benefits should be weighed against potential risks. • Drug treatment of severe hypertension in pregnancy (SBP >160 mmHg or DBP >110 mmHg) is recommended. • Drug treatment may also be considered in pregnant women with persistent elevation of BP ≥150/95 mmHg, and in those with BP ≥140/90 mmHg in the presence of gestational hypertension, subclinical organ damage or symptoms. • In women at high risk of pre-eclampsia, provided they are at low risk of gastrointestinal hemorrhage, treatment with low dose aspirin from 12 weeks until delivery may be considered. • In women with child-bearing potential RAS blockers are not recommended and should be avoided. • Methyldopa, labetalol, and nifedipine should be considered preferential antihypertensive drugs in pregnancy. Intravenous labetalol or infusion of nitroprusside should be considered in case of emergency (pre-eclampsia). <u>Treatment strategies in patients with diabetes</u> • While initiation of antihypertensive drug treatment in diabetic patients whose SBP is ≥160 mmHg is mandatory, it is strongly recommended to start drug treatment also when SBP is ≥140 mmHg. • A SBP goal <140 mmHg is recommended in patients with diabetes. • The DBP target in patients with diabetes is recommended to be <85 mmHg. • All classes of antihypertensive agents are recommended and can be used in patients with diabetes; RAS blockers may be preferred, especially in the presence of proteinuria or microalbuminuria. • It is recommended that individual drug choice takes comorbidities into account. • Simultaneous administration of two blockers of the RAS is not recommended and should be avoided in patients with diabetes <u>Treatment strategies in hypertensive patients with metabolic syndrome</u> • Lifestyle changes, particularly weight loss and physical exercise, are to be recommended to all individuals with the metabolic syndrome. These interventions improve not only BP, but the metabolic components of the syndrome and delay diabetes onset. • As the metabolic syndrome can be considered a 'pre-diabetic' state, antihypertensive agents potentially improving or at least not worsening insulin sensitivity, such as RAS blockers and calcium antagonists, should be considered as the preferred drugs. Beta-blockers (with the exception of vasodilating β-blockers) and diuretics should be considered only as additional drugs, preferably in association with a potassium-sparing agent. • It is recommended to prescribe antihypertensive drugs with particular care in hypertensive patients with metabolic disturbances when BP is ≥140/90 mmHg after a suitable period of lifestyle changes, and to maintain BP <140/90 mmHg. • BP lowering drugs are not recommended in individuals with metabolic syndrome and high normal BP. <u>Therapeutic strategies in hypertensive patients with nephropathy</u> • Lowering SBP to <140 mmHg should be considered.

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	• When overt proteinuria is present, SBP values <130 mmHg may be considered, provided that changes in eGFR are monitored. • RAS blockers are more effective in reducing albuminuria than other antihypertensive agents, and are indicated in hypertensive patients in the presence of microalbuminuria or overt proteinuria. • Reaching BP goals usually requires combination therapy, and it is recommended to combine RAS blockers with other antihypertensive agents. • Combination of two RAS blockers, though potentially more effective in reducing proteinuria, is not recommended. • Aldosterone antagonists cannot be recommended in chronic kidney disease (CKD), especially in combination with a RAS blocker, because of the risk of excessive reduction in renal function and of hyperkalemia. <u>Therapeutic strategies in hypertensive patients with cerebrovascular disease</u> • It is not recommended to intervene with BP-lowering therapy during the first week after acute stroke irrespective of BP level, although clinical judgement should be used in the face of very high SBP values. • Antihypertensive treatment is recommended in hypertensive patients with a history of stroke or transient ischemic attack (TIA), even when initial SBP is in the 140 to 159 mmHg range. • In hypertensive patients with a history of stroke or TIA, a SBP goal of <140 mmHg should be considered. • In elderly hypertensives with previous stroke or TIA, SBP values for intervention and goal may be considered to be somewhat higher. • All drug regimens are recommended for stroke prevention, provided that BP is effectively reduced. <u>Therapeutic strategies in hypertensive patients with heart disease</u> • In hypertensive patients with CHD, a SBP goal <140 mmHg should be considered. • In hypertensive patients with a recent myocardial infarction, β-blockers are recommended. In case of other CHD all antihypertensive agents can be used, but β-blockers and calcium antagonists are to be preferred for symptomatic reasons (angina). • Diuretics, β-blockers, ACE inhibitors, angiotensin receptor blockers, and/or mineralocorticoid receptor antagonists are recommended in patients with heart failure or severe left ventricular (LV) dysfunction to reduce mortality and hospitalization. • In patients with heart failure and preserved ejection fraction (EF), there is no evidence that antihypertensive therapy per se or any particular drug is beneficial. However, in these patients, as well as in patients with hypertension and systolic dysfunction, lowering SBP to around 140 mmHg should be considered. Treatment guided by relief of symptoms (congestion with diuretics, high heart rate with β-blockers, etc.) should also be considered. • ACE inhibitors and angiotensin receptor blockers (and β-blockers and mineralocorticoid receptor antagonists if heart failure coexists) should be considered as antihypertensive agents in patients at risk of new or recurrent atrial fibrillation. • It is recommended that all patients with left ventricular hypertrophy (LVH) receive antihypertensive agents. • In patients with LVH, initiation of treatment with one of the agents that have shown a greater ability to regress LVH should be considered, i.e. ACE inhibitors, angiotensin receptor blockers, and calcium antagonists. <u>Therapeutic strategies in hypertensive patients with atherosclerosis, arteriosclerosis,</u>

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	and peripheral artery disease (PAD) • In the presence of carotid atherosclerosis, prescription of calcium antagonists and ACE inhibitors should be considered as these agents have shown a greater efficacy in delaying atherosclerosis progression than diuretics and β-blockers. • In hypertensive patients with a pulse wave velocity above 10 m/s, all antihypertensive drugs should be considered provided that a BP reduction to <140/90 mmHg is consistently achieved. • Antihypertensive therapy is recommended in hypertensive patients with PAD to achieve a goal of <140/90 mmHg, because of their high risk of myocardial infarction, stroke, heart failure, and CV death. ○ Though a careful follow up is necessary, β-blockers may be considered for the treatment of arterial hypertension in patients with PAD, since their use does not appear to be associated with exacerbation of PAD symptoms.

National Institute for Health and Clinical Excellence: **Hypertension in adults: diagnosis and management (2011)[17]**
 	
Reaffirmed Nov 2016
	Choosing antihypertensive drug treatment
	• 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 people ≥80 years of age the same antihypertensive drug treatment as people aged 55 to 80 years, taking into account any comorbidities.
	• Offer antihypertensive drug treatment to women of child-bearing potential in line with the recommendations on Management of pregnancy with chronic hypertension and Breastfeeding in 'Hypertension in pregnancy' (NICE clinical guideline 107).
	
	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). 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 step one antihypertensive (ACE inhibitor, ARB) with a calcium channel blocker (CCB) to patients >55 years of age and to black patients of African or Caribbean family origin 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 chlorthalidone (12.5 to 25.0 mg once daily) or indapamide (1.5 mg modified-release once daily or 2.5 mg once daily) in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide.
	• For patients who are already receiving treatment with bendroflumethiazide or hydrochlorothiazide and whose blood pressure is stable and well controlled, continue treatment as is.
	• β-blockers are not a preferred initial therapy for hypertension; however, β-blockers may be considered in younger patients, particularly:
	  ○ Patients with an intolerance or contraindication to ACE inhibitors and ARBs.
	  ○ Women of child-bearing potential.
	  ○ People with evidence of increased sympathetic drive.
	• If treatment is initiated with a β-blocker and a second antihypertensive is required, add a CCB over a thiazide-like diuretic to reduce the risk of developing diabetes.

Clinical Guideline	Recommendation(s)

	Step two treatment
	• If blood pressure is not controlled with a step one antihypertensive, offer a step two treatment with a CCB in combination with an ACE inhibitor or an ARB.
	• If a CCB is not appropriate or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic.
	• For black patients of African or Caribbean family origin, consider an ARB in preference to an ACE inhibitor, in combination with a CCB.
	
	Step three treatment
	• Before considering step three treatment, review medication to ensure step two treatment is at optimal or best tolerated doses.
	• If three drugs are required to control blood pressure, the combination of an ACE inhibitor or ARB, CCB, and thiazide-like diuretic should be utilized.
	
	Step four treatment
	• Regard clinic blood pressure that remains >140/90 mmHg after treatment with the optimal or best tolerated doses of an ACE inhibitor or an ARB plus a CCB plus a diuretic as resistant hypertension, and consider adding a fourth antihypertensive drug and/or seeking expert advice.
	• For treatment of resistant hypertension at step four:
	  ○ Consider further diuretic therapy with low-dose spironolactone (25 mg once daily) if the blood potassium level is 4.5 mmol/l or lower. Use particular caution in people with a reduced estimated glomerular filtration rate because they have an increased risk of hyperkalemia.
	  ○ Consider higher-dose thiazide-like diuretic treatment if the blood potassium level is higher than 4.5 mmol/l.
	• If further diuretic therapy for resistant hypertension is not tolerated or is contraindicated or ineffective, consider an α-blocker or β-blocker.

International Society on Hypertension in Blacks: **Management of High Blood Pressure in Blacks (2010)**[18]	• 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**	Blood pressure management in chronic kidney disease (CKD) non-dialysis (ND) patients without diabetes mellitus • The Work Group recommends that non-diabetic adults with CKD ND and urine

Clinical Guideline	Recommendation(s)
Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease (2012)[19]	albumin excretion <30 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >140 mm Hg systolic or >90 mm Hg diastolic be treated with blood pressure -lowering drugs to maintain a blood pressure that is consistently ≤140 mm Hg systolic and ≤90 mm Hg diastolic. • The Work Group suggests that non-diabetic adults with CKD ND and urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with BP-lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic. • The Work Group suggests that non-diabetic adults with CKD ND and urine albumin excretion >300 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with blood pressure -lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤ 80 mm Hg diastolic. • The Work Group suggests that an angiotensin receptor blocker (ARB) or angiotensin converting enzyme inhibitor (ACE-I) be used in non-diabetic adults with CKD ND and urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*) in whom treatment with blood pressure -lowering drugs is indicated. • The Work Group recommends that an ARB or ACE-I be used in non-diabetic adults with CKD ND and urine albumin excretion >300 mg per 24 hours (or equivalent*) in whom treatment with blood pressure -lowering drugs is indicated. <u>Blood pressure management in CKD ND patients with diabetes mellitus</u> • The Work Group recommends that adults with diabetes and CKD ND with urine albumin excretion <30 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >140 mm Hg systolic or >90 mm Hg diastolic be treated with BP-lowering drugs to maintain a blood pressure that is consistently ≤140 mm Hg systolic and ≤90 mm Hg diastolic. • The Work Group suggests that adults with diabetes and CKD ND with urine albumin excretion >30 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with BP-lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic. • The Work Group suggests that an ARB or ACE-I be used in adults with diabetes and CKD ND with urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*). • The Work Group recommends that an ARB or ACE-I be used in adults with diabetes and CKD ND with urine albumin excretion >300 mg per 24 hours (or equivalent*). <u>Blood pressure management in kidney transplant recipients (non–dialysis-dependent CKD of any stage with a kidney transplant [CKD T])</u> • The Work Group suggests that adult kidney transplant recipients whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic, irrespective of the level of urine albumin excretion. • In adult kidney transplant recipients, choose a blood pressure -lowering agent after taking into account the time after transplantation, use of calcineurin inhibitors, presence or absence of persistent albuminuria, and other co morbid conditions. <u>Blood pressure management in children with CKD ND</u> • The Work Group recommends that in children with CKD ND, blood pressure -lowering treatment is started when blood pressure is consistently above the 90th percentile for age, sex, and height.

Clinical Guideline	Recommendation(s)
	• The Work Group suggests that in children with CKD ND (particularly those with proteinuria), blood pressure is lowered to consistently achieve systolic and diastolic readings less than or equal to the 50th percentile for age, sex, and height, unless achieving these targets is limited by signs or symptoms of hypotension. • The Work Group suggests that an ARB or ACE-I be used in children with CKD ND in whom treatment with blood pressure -lowering drugs is indicated, irrespective of the level of proteinuria. Blood pressure management in elderly persons with CKD ND • Tailor blood pressure treatment regimens in elderly patients with CKD ND by carefully considering age, co-morbidities and other therapies, with gradual escalation of treatment and close attention to adverse events related to blood pressure treatment, including electrolyte disorders, acute deterioration in kidney function, orthostatic hypotension and drug side effects. *Approximate equivalents for albumin excretion rate per 24 hours is expressed as protein excretion rate per 24 hours, albumin/creatinine ratio, protein/creatinine ratio, and protein reagent strip results.
American Diabetes Association: **Standards of Medical Care in Diabetes (2017)**[20]	Hypertension/blood pressure control • Blood pressure should be measured at every routine visit. Patients found to have elevated blood pressure should have blood pressure confirmed on a separate day. • Most patients with diabetes and hypertension should be treated to a systolic blood pressure goal of <140 mmHg and a diastolic blood pressure goal of <90 mmHg. • Lower systolic and diastolic blood pressure targets, such as 130/80 mmHg, may be appropriate for individuals at high risk of cardiovascular disease, if they can be achieved without undue treatment burden. • In pregnant patients with diabetes and chronic hypertension, blood pressure targets of 120 to 160/80 to 105 mmHg are suggested in the interest of optimizing long-term maternal health and minimizing impaired fetal growth. • Patients with confirmed office-based blood pressure >140/90 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). 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. • For patients with blood pressure >120/80 mmHg, lifestyle intervention consists of weight loss if overweight or obese; a Dietary Approaches to Stop Hypertension–style dietary pattern including reducing sodium and increasing potassium intake; moderation of alcohol intake; and increased physical activity.

Clinical Guideline	Recommendation(s)
	Coronary heart disease • In asymptomatic patients, routine screening for coronary artery disease is not recommended as it does not improve outcomes as long as atherosclerotic cardiovascular disease risk factors are treated. • Consider investigations for coronary artery disease in the presence of any of the following: atypical cardiac symptoms (e.g., unexplained dyspnea, chest discomfort); signs or symptoms of associated vascular disease including carotid bruits, transient ischemic attack, stroke, claudication, or peripheral arterial disease; or electrocardiogram abnormalities (e.g., Q waves). • In patients with known atherosclerotic cardiovascular disease, use aspirin and statin therapy (if not contraindicated) and consider ACE inhibitor therapy to reduce the risk of cardiovascular events. • In patients with prior myocardial infarction, β-blockers should be continued for at least two years after the event. • In patients with symptomatic heart failure, thiazolidinedione treatment should not be used. • In patients with type 2 diabetes with stable congestive heart failure, metformin may be used if estimated glomerular filtration remains >30 mL/min but should be avoided in unstable or hospitalized patients with congestive heart failure. Diabetic 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, in all patients with type 2 diabetes, and in all patients with comorbid hypertension. • Optimize glucose control to reduce the risk or slow the progression of diabetic kidney disease. • Optimize blood pressure control to reduce the risk or slow the progression of diabetic kidney disease. • For people with nondialysis-dependent diabetic kidney disease, dietary protein intake should be approximately 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. • 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) B 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 or changes in potassium when ACE inhibitors, angiotensin receptor blockers, or diuretics are used. • Continued monitoring of urinary albumin–to–creatinine ratio in patients with albuminuria treated with an ACE inhibitor or an angiotensin receptor blocker is reasonable to assess the response to treatment and progression of diabetic kidney disease. • An ACE inhibitor or an angiotensin receptor blocker is not recommended for the primary prevention of diabetic kidney disease 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. • When estimated glomerular filtration rate is <60 mL/min/1.73 m^2, evaluate and manage potential complications of chronic kidney disease. • Patients should be referred for evaluation for renal replacement treatment if they have an estimated glomerular filtration rate <30 mL/min/1.73 m^2. • Promptly refer to a physician experienced in the care of kidney disease for

Clinical Guideline	Recommendation(s)
	uncertainty about the etiology of kidney disease, difficult management issues, and rapidly progressing kidney disease.
American Association for the Study of Liver Diseases: **Management of Adult Patients with Ascites Due to Cirrhosis: Update 2012 (2012)**[21] **[Reaffirmed Oct 2014]**	Treatment of ascites • First line treatment of patients with cirrhosis and ascites consists of sodium restriction (88 mmol/day [2,000 mg/day]) and diuretics (oral spironolactone with or without oral furosemide). • Fluid restriction is not necessary unless serum sodium is <125 mmol/L. • Vasopressin antagonists may improve serum sodium in patients with cirrhosis and ascites. However their use does not currently appear justified in view of their expense, potential risks, and lack of evidence of efficacy in clinically meaningful outcomes. • An initial therapeutic abdominal paracentesis should be performed in patients with tense ascites. Sodium restriction and oral diuretics should then be initiated. • Diuretic-sensitive patients should preferably be treated with sodium restriction and oral diuretics rather than with serial paracentesis. • Use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers in patients with cirrhosis and ascites may be harmful and must be carefully considered in each patient, monitoring blood pressure and renal function. • The use of nonsteroidal anti-inflammatory drugs should be avoided in patients with cirrhosis and ascites, except in special circumstances. • Liver transplantation should be considered in patients with cirrhosis and ascites.

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[3-6]

Indication	Bumetanide	Ethacrynic Acid	Furosemide	Torsemide
Edema				
Adjunctive therapy in acute pulmonary edema			✔ * (injection)	
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 medication 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.

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	-	✔	✔
Shunt thrombosis	-	-	-	✔
Syncope	-	-	-	✔

Adverse Events	Bumetanide	Ethacrynic Acid	Furosemide	Torsemide
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				
Agranulocytosis	-	✔	✔	-
Anemia	-	-	✔	-

Adverse Events	Bumetanide	Ethacrynic Acid	Furosemide	Torsemide
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				
Cough	-	-	-	2
Hyperventilation	<1	-	-	-

Adverse Events	Bumetanide	Ethacrynic Acid	Furosemide	Torsemide
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 the Loop Diuretics (excluding torsemide)[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: Tablet: initial, 25 mg/kg; maximum, 3 mg/kg/day	Tablet: 25 mg
Furosemide	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	Edema: Injection: initial, 1 mg/kg; maintenance, may increase by 1 mg/kg not sooner than two hours after the previous dose; maximum, 6 mg/kg per dose Solution, tablet: 2 mg/kg as	Injection: 10 mg/mL Solution: 10 mg/ mL 40 mg/5 mL Tablet: 20 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	increased by 20 mg until desired response Oral: 20 to 80 mg/days; maximum, 600 mg/day Hypertension: Injection, solution, tablet: 80 mg/day	a single dose; maximum, 6 mg/kg per dose	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:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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
Levy et al.[36] (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
Austin et al.[37] (1976) Furosemide 40 to 60 mg infused through a pulmonary artery catheter vs ethacrynic acid 25 to 50 mg infused through a pulmonary artery	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	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
catheter			Secondary: Not reported	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.[38] (1994) Torsemide 5 mg QD vs torsemide 10 mg QD vs torsemide 20 mg QD vs placebo QD	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.
Senzaki et al.[39] (2008) Torasemide* (de novo group) vs torasemide*	RCT Pediatric patients (age range from 3 weeks to 17 years) with congested heart failure, patients newly diagnosed with	N=102 3 to 4 weeks	Primary: Clinical signs and symptoms of congestive heart failure Secondary: Humoral factors, serum potassium	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(replacement group) was converted from furosemide dosage using 0.2 mg torasemide* corresponding to 1 mg furosemide	CHF or previously treated with furosemide		levels, and adverse events	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.[40] (2006) Loop diuretics (furosemide, bumetanide), thiazide diuretics (chlorothiazide), or potassium-sparing diuretics (amiloride, triamterene) vs placebo or active control (ACE inhibitors, digoxin)	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). 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.[41] (1998) Bumetanide 1 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	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-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs furosemide 40 mg/day for 6 weeks			Secondary: Not reported	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.[42] (2007) Furosemide infused in 3 progressive solutions containing 475, 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	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. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
arterial studies and 200, 400, and 800 nmol/mL for venous studies				
von Dossow et al.[43] (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.[44] (2003) <u>Phase 1: Inpatient</u> Furosemide 200 mg/day with sodium-free water (10 mL/kg) vs torsemide 100 mg/day with sodium-free water (10 mL/kg)	DB, RCT, two-phase, XO Patients ≥18 years of age with chronic kidney disease (serum creatinine >1.4 mg/dL) and volume overload	N=14 3 weeks	Primary: <u>Phase 1: Inpatient</u> Change in 24-hour urinary sodium excretion <u>Phase 2: Outpatient</u> Primary: 24-hour ambulatory SBP Secondary: Potassium, calcium, protein excretion, diurnal variation of	Primary <u>Phase 1: Inpatient</u> 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. <u>Phase 2: Outpatient</u> 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Phase 2:Outpatient Furosemide 80 mg/day vs torsemide 40 mg/day			electrolyte and protein excretion, and glomerular filtration rate	
Pupita et al.[45] (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 (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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Valmin K et al.[46] (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: 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.[47] (2006) Furosemide 20 mg/day plus	PRO, RCT Adult patients with HTN and type 2 diabetes, with a	N=30 24 months	Primary: Change in BNP, urine albumin/ creatinine ratio, and blood pressure	Primary: At 12 months, spironolactone-treated patients exhibited a significant reduction in BNP level from baseline compared to furosemide-treated patients (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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.	urine albumin/ creatinine ratio >30 mg/g creatinine, and plasma BNP levels >100 pg/mL (suggestive of mild heart failure)		Secondary: Not reported	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.[48] (2008) Spironolactone 25 mg/day (triple blockade group) 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.	MC, OL, PRO, RCT Patients 20 to 70 years of age, with controlled blood pressure <130/80 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	N=32 12 months	Primary: Reduction in proteinuria, urinary type IV collagen, SBP, DBP, mean blood pressure, creatinine, creatinine clearance, potassium, urinary aldosterone Secondary: Not reported	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 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	>0.5 g/day)			
Hannson et al.[49] (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.[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)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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.[51] (2007) Loop diuretics (frusemide†, torasemide*) vs placebo	MA Patients with acute renal failure	N=555 Variable duration	Primary: Mortality, need for renal replacement therapy, and renal recovery Secondary: Urine output, serum potassium level and acid-base status, duration of acute renal failure or renal replacement therapy, length of hospital stay, toxicity	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 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.[52] (2006)	DB, PC, RCT, XO Men and women	N=16 14 days	Primary: Patient reported quality of life	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Bumetanide 0.5 mg (0, 1, 2, or 4 tablets BID) vs trandolapril 0.5 mg (0, 1, 2, or 4 tablets QD)	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)		Secondary: Effects on the involved organs: kidney function, left ventricular function, blood pressure	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	$$$
Ethacrynic acid	tablet	Edecrin®*	$$$$$	$$$$$
Furosemide	injection, solution, tablet	Lasix®*	$	$
Torsemide	tablet	Demadex®*	$$$	$

*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.[3-6] 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 is an alternative treatment option in patients experiencing gynecomastia with spironolactone.

Triamterene, metolazone, and hydrochlorothiazide have also been used to treat ascites.[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.[10-12] 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] The most commonly used loop diuretic for the treatment of heart failure is furosemide; however, some patients may respond more favorably to other agents. Torsemide is better absorbed than furosemide and has a longer duration of action. It may be appropriate to use in patients exhibiting an erratic diuretic effect and in those with refractory fluid retention despite high doses of other loop diuretics.[11]

There are several published guidelines on the treatment of hypertension. Thiazide-type diuretics are frequently recommended as initial therapy in patients with uncomplicated hypertension.[13-19] 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).[13] Several guidelines consistently recommend that the selection of an antihypertensive agent be based on compelling indications for use.[13-19] Most patients will require more than one antihypertensive medication to achieve blood pressure goals.[13-19]

In clinical trials, the thiazide diuretics have been shown to effectively lower blood pressure.[41-50] 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.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Potassium-Sparing Diuretics
AHFS Class 402816
November 8, 2017

I. Overview

The potassium-sparing diuretics are approved for the treatment of congestive heart failure, edema, and hypertension.[1-4] 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.[1-8] When used alone, potassium-sparing diuretics have a weak diuretic and antihypertensive effect and increased risk of hyperkalemia.[4] 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.[1-4] 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.[5-8]

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 with the exception of single-entity triamterene are available in a generic formulation. This class was last reviewed in August 2015.

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	Dyrenium®	none
Combination Products			
Amiloride and hydrochlorothiazide	tablet	N/A	amiloride and hydrochlorothiazide
Triamterene and hydrochlorothiazide	capsule, tablet	Dyazide®*, Maxzide®*	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 College of Cardiology/American Heart Association: **Guideline for the Management of Heart Failure (2013)[9]**	<u>Treatment of Stage A heart failure (HF)</u> • Hypertension and lipid disorders should be controlled in accordance with guidelines to lower the risk of HF. (Level of Evidence (LoE): A) • Other conditions that may lead to or contribute to HF, such as obesity, diabetes mellitus, tobacco use, and known cardiotoxic agents, should be controlled or avoided. (LoE: C) <u>Treatment of Stage B heart failure</u> • In patients with a history of MI and reduced EF, ACE inhibitors or ARBs should be used to prevent HF. (LoE: A) • In patients with MI and reduced EF, evidence-based β-blockers (using one of three proven to reduce mortality [i.e., bisoprolol, carvedilol, and sustained-

Clinical Guideline	Recommendation(s)
	release metoprolol succinate]) should be used to prevent HF. (LoE: B) • In patients with MI, statins should be used to prevent HF. (LoE: A) • ACE inhibitors and β-blockers should be used in all patients with a reduced EF to prevent symptomatic HF, even if they do not have a history of MI. (LoE: A and C, respectively) • Blood pressure should be controlled to prevent symptomatic HF. (LoE: A) • Nondihydropyridine calcium channel blockers may be harmful in patients with low LVEF. (LoE: C) <u>Pharmacological treatment for Stage C HFrEF</u> • Recommendations for patients in Stages A and B are recommended where appropriate for patients in Stage C. (LoE: A, B, and C as appropriate) • Diuretics are recommended in patients with HFrEF who have evidence of fluid retention, unless contraindicated, to improve symptoms. (LoE: C) • ACE inhibitors are recommended in patients with HFrEF and current or prior symptoms, unless contraindicated, to reduce morbidity and mortality. ARBs are recommended as alternative therapy in ACE inhibitor intolerant patients. (LoE: A) • Use of one of the three β-blockers proven to reduce mortality is recommended for all patients with current or prior symptoms of HFrEF, unless contraindicated, to reduce morbidity and mortality. (LoE: A) • Aldosterone receptor antagonists are recommended in patients with NYHA class II–IV HF and who have LVEF of ≤35%, unless contraindicated, to reduce morbidity and mortality. Patients with NYHA class II HF should have a history of prior cardiovascular hospitalization or elevated plasma natriuretic peptide levels to be considered for aldosterone receptor antagonists. Creatinine should be ≤2.5 mg/dL in men or ≤2.0 mg/dL in women (or estimated glomerular filtration rate >30 mL/min/1.73 m^2), and potassium should be <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) • The combination of hydralazine and isosorbide dinitrate is recommended to reduce morbidity and mortality for patients self-described as African Americans with NYHA class III–IV HFrEF receiving optimal therapy with ACE inhibitors and β-blockers, unless contraindicated. (LoE: A) • Digoxin can be beneficial in patients with HFrEF, unless contraindicated, to decrease hospitalizations for HF. (LoE: B) • Patients with chronic HF with permanent/persistent/paroxysmal AF and an additional risk factor for cardioembolic stroke (history of hypertension, diabetes mellitus, previous stroke or transient ischemic attack, or ≥75 years of age) should receive chronic anticoagulant therapy. (LoE: A) • Statins are not beneficial as adjunctive therapy when prescribed solely for the diagnosis of HF in the absence of other indications for their use. (LoE: A) • Calcium channel blockers are not recommended as routine treatment for patients with HFrEF. (LoE: A) <u>Pharmacological treatment for Stage C HFpEF</u> • Blood pressure should be controlled according to published clinical practice guidelines. (LoE: B) • Diuretics should be used for relief of symptoms due to volume overload. (LoE: C) • The use of β-blocking agents, ACE inhibitors, and ARBs in patients with hypertension is reasonable to control blood pressure in patients with HFpEF. (LoE: C)

Clinical Guideline	Recommendation(s)
	Treatment of Stage D (advanced/refractory) HF • Fluid restriction (1.5 to 2 L/d) is reasonable, especially in patients with hyponatremia, to reduce congestive symptoms. (LoE: C) • Until definitive therapy (e.g., coronary revascularization, mechanical circulatory support, heart transplantation) or resolution of the acute precipitating problem, patients with cardiogenic shock should receive temporary intravenous inotropic support to maintain systemic perfusion and preserve end-organ performance. (LoE: C) • Continuous intravenous inotropic support is reasonable as "bridge therapy" in patients with stage D HF refractory to medical therapy and device therapy who are eligible for and awaiting mechanical circulatory support or cardiac transplantation. (LoE: B) • Long-term use of either continuous or intermittent, intravenous parenteral positive inotropic agents, in the absence of specific indications or for reasons other than palliative care, is potentially harmful in the patient with HF. (LoE: B)
Heart Failure Society of America: **Heart Failure Society of America 2010 Comprehensive Heart Failure Practice Guidelines (Executive Summary) (2010)[10]**	Patients with left ventricular systolic dysfunction • ACE inhibitors should be used in all patients with a LVEF ≤40%, unless otherwise contraindicated. • ARBs may be used in patients who are intolerant to ACE inhibitors. Hydralazine and a nitrate may be used in patients intolerant to ACE inhibitors and ARBs, or in whom such therapy is contraindicated. • The combination of an ACE inhibitor and a β-blocker is recommended in all patients with a LVEF ≤40%. • The routine use of an ARB with a combination of an ACE inhibitor and β-blocker in patients who have had a MI and have left ventricular dysfunction is not recommended. • The addition of an ARB can be considered in patients with heart failure due to reduced LVEF who have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor and a β-blocker. • Individual ARBs may be considered as initial therapy (instead of an ACE inhibitor) in patients with heart failure who have had a MI and in patients with chronic heart failure and systolic dysfunction. • ARBs are recommended in patients who cannot tolerate ACE inhibitors due to cough. The combination of hydralazine and an oral nitrate may be considered in such patients not tolerating ARB therapy. • Patients intolerant to ACE inhibitors from hyperkalemia or renal insufficiency are likely to experience the same side effects with ARBs. In these cases, the combination of hydralazine and an oral nitrate should be considered. • ARBs should be considered in patients experiencing angioedema while on ACE inhibitors based on their underlying risk and with recognition that angioedema has been reported infrequently with ARBs. The combination of hydralazine and oral nitrates may be considered in such patients not tolerating ARB therapy. • A combination of hydralazine and an oral nitrate is recommended in African American patients with heart failure and reduced left ventricular ejection fraction (LVEF) who are on a standard regimen of an ACE inhibitor (or ARB) and a β-blocker. • A combination of hydralazine and an oral nitrate may be considered in non–African American patients with heart failure and reduced LVEF who are symptomatic despite optimization of standard therapy. • Administration of an aldosterone antagonist is recommended for patients with New York Heart Association (NYHA) class IV (or class III, previously class IV) heart failure from reduced LVEF (<35%) while receiving standard therapy, including diuretics. • Administration of an aldosterone antagonist should be considered in patients following an acute MI, with clinical heart failure signs and symptoms or history

Clinical Guideline	Recommendation(s)
	of diabetes mellitus, and an LVEF <40%. Patients should be on standard therapy, including an ACE inhibitor (or ARB) and a β-blocker. • The triple combination of an ACE inhibitor, an ARB, and an aldosterone antagonist is not recommended because of the high risk of hyperkalemia. <u>Patients with hypertension and symptomatic left ventricular dysfunction with left ventricular dilation and low LVEF</u> • ACE inhibitors, ARBs, β-blockers, aldosterone inhibitors, and isosorbide dinitrate/hydralazine in various combinations (with a loop diuretic if needed) are recommended. • If blood pressure remains >130/80 mm Hg, a dihydropyridine calcium channel blocker (e.g., amlodipine or felodipine) may be considered or other antihypertensive medication doses increased. <u>Managing heart failure in special populations</u> • The combination of hydralazine/isosorbide dinitrate is recommended for African American women with moderate to severe heart failure symptoms who are on background neurohormonal inhibition. • A combination of hydralazine and isosorbide dinitrate is recommended as part of standard therapy in addition to β-blockers and ACE-inhibitors for African Americans with left ventricular systolic dysfunction and NYHA class II-IV heart failure. • As in all patients, but especially in the elderly, careful attention to volume status, the possibility of symptomatic cerebrovascular disease and the presence of postural hypotension are recommended during therapy with ACE inhibitors, β-blockers and diuretics. <u>Patients with heart failure and preserved LVEF</u> • ACE inhibitors or ARBs should be considered in this patient population. • ACE inhibitors should be considered in patients with heart failure and symptomatic atherosclerotic cardiovascular disease or diabetes and at least one other risk factor. ARBs may be used in patients who are intolerant to ACE inhibitors. • Beta-blocker treatment is recommended in patients with HF and preserved LVEF who have prior MI, hypertension, or AF. • Calcium channel blockers should be considered in patients with heart failure and preserved LVEF who have atrial fibrillation requiring ventricular rate control and intolerance to β-blockers (consider diltiazem or verapamil), symptom-limiting angina, or hypertension. • Diuretic therapy is recommended in all patients with heart failure and clinical evidence of volume overload, including those with preserved LVEF. • Treatment may begin with either a thiazide or loop diuretic. In more severe volume overload or if response to a thiazide is inadequate, treatment with a loop diuretic should be implemented. • Excessive diuresis, which may lead to orthostatic changes in blood pressure and worsening renal function, should be avoided. <u>Patients with heart failure and CAD</u> • Calcium channel blockers should be considered in patients who have angina despite optimization of β-blocker and nitrates. Amlodipine and felodipine are preferred in patients with decreased systolic function. <u>Patients with heart failure and hypertension</u> • Patients with left ventricular hypertrophy or left ventricular dysfunction without left ventricular dilation should be treated to a goal blood pressure of <130/80

Clinical Guideline	Recommendation(s)
	mm Hg. Treatment with several drugs may be necessary, including an ACE inhibitor (or ARB), a diuretic and a β-blocker or calcium channel blocker. • Patients with asymptomatic left ventricular dysfunction and left ventricular dilation and a reduced ejection fraction should receive an ACE inhibitor and a β-blocker. If blood pressure remains elevated (>130/80 mm Hg), the addition of a diuretic is recommended, followed by a calcium channel blocker or other antihypertensive agent. • If blood pressure remains >130/80 mm Hg, then the addition of a thiazide diuretic is recommended, followed by a dihydropyridine calcium channel blocker (e.g., amlodipine or felodipine) or other antihypertensive drugs. <u>Patients at risk for development of heart failure</u> • ACE inhibitors are recommended in patients who are at risk for the development of heart failure including patients with CAD, peripheral vascular disease, stroke, diabetes and another major risk factor, and patients with diabetes who smoke and have microalbuminuria. <u>Patients with asymptomatic heart failure and reduced LVEF</u> • ACE inhibitors are recommended in asymptomatic patients with reduced LVEF (<40%). • ARBs may be used in patients who are intolerant to ACE inhibitors. • Routine use of a combination of ACE inhibitors and ARBs is not recommended. • β-blocker therapy should be considered. <u>Patients with heart failure and ischemic heart disease</u> • ACE inhibitor therapy is recommended in all patients with either reduced or preserved LVEF after a MI. • Beta-blockers are recommended for the management of all patients with reduced LVEF or post-MI. • ACE inhibitor and β-blocker therapy should be initiated early (<48 hours) during hospitalization in hemodynamically stable patients who are post-MI with reduced LVEF or heart failure. • Calcium channel blockers may be considered in patients with HF who have angina despite the optimal use of β-blockers and nitrates. <u>Managing heart failure in the elderly, women and African Americans</u> • Standard regimens of ACE inhibitors and β-blockers are recommended in elderly patients with heart failure. • ACE inhibitor and β-blocker therapy are recommended in all women with heart failure and left ventricular systolic dysfunction. • ACE inhibitor and β-blocker therapy are recommended in all African American patients with heart failure and left ventricular systolic dysfunction. ARBs may be substituted in patients who are intolerant to ACE inhibitors. <u>Heart failure in patients with reduced ejection fraction</u> • ACE inhibitors are recommended in asymptomatic patients with reduced LVEF (<40%). • ARBs may be used in patients who are intolerant to ACE inhibitors. • β-blockers shown to be effective in clinical trials of patients with heart failure are recommended for patients with a LVEF ≤40%. • The combination of a β-blocker and an ACE inhibitor is recommended as routine therapy for asymptomatic patients with a LVEF ≤40%. The evidence is stronger in patients with a history of MI. • β-blocker therapy is recommended for patients with a recent decompensation of heart failure after optimization of volume status and successful discontinuation

Clinical Guideline	Recommendation(s)
	of intravenous diuretics and vasoactive drugs. Whenever possible, β-blocker therapy should be initiated in the hospital setting at a low dose prior to discharge of stable patients. • β-blocker therapy is recommended in the great majority of patients with heart failure and reduced LVEF, even if there is concurrent diabetes, chronic obstructive pulmonary disease or peripheral vascular disease. Caution may be warranted in these patients. • It is recommended that β blockade be initiated at low doses and uptitrated gradually. • It is recommended that β-blocker therapy be continued in most patients experiencing a symptomatic exacerbation of heart failure during chronic maintenance treatment, unless they develop cardiogenic shock, refractory volume overload or symptomatic bradycardia. • The routine use of an ARB is not recommended in addition to an ACE inhibitor and a β-blocker in patients with a recent acute MI and reduced LVEF. • The addition of an ARB should be considered in patients with heart failure due to reduced LVEF who have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor and a β-blocker. • Administration of an aldosterone antagonist is recommended for patients with NYHA class IV (or class III, previously class IV) HF from reduced LVEF (<35%) while receiving standard therapy, including diuretics. • Diuretic therapy is recommended to restore and maintain normal volume status in patients with clinical evidence of fluid overload, generally manifested by congestive symptoms or signs of elevated filling pressures. Loop diuretics rather than thiazide-type diuretics are typically necessary to restore normal volume status in patients with heart failure. • The initial dose of diuretic may be increased as necessary to relieve congestion, and restoration of normal volume status may require multiple adjustments, especially in patients with severe fluid overload evidenced by massive edema or ascites. After a diuretic effect is achieved with loop diuretics (short acting), increasing administration frequency to twice or even three times/day will provide more diuresis with less physiologic perturbation than larger single doses. • Oral torsemide may be considered in patients in whom poor absorption of oral medication or erratic diuretic effect may be present. Particularly in patients with right-sided heart failure and refractory fluid retention despite high doses of other loop diuretics. • Intravenous administration of diuretics may be necessary to relieve congestion. • Diuretic refractoriness may represent patient nonadherence, a direct effect of diuretic use on the kidney or progression of underlying cardiac dysfunction. • Addition of chlorothiazide or metolazone, once or twice daily, to loop diuretics should be considered in patients with persistent fluid retention despite high dose loop diuretic therapy. Chronic daily use should be avoided if possible because of the potential for electrolyte shifts and volume depletion. These drugs may be used periodically (every other day or weekly) to optimize fluid management. Metolazone will generally be more potent and much longer acting in this setting and in patients with chronic renal insufficiency, so administration should be adjusted accordingly. Volume status and electrolytes must be monitored closely when multiple diuretics are used. • Careful observation for the development of side effects is recommended in patients treated with diuretics, especially when high doses or combination therapy are used. Patients should undergo routine laboratory studies and clinical examination as dictated by their clinical response. • Patients requiring diuretic therapy to treated fluid retention associated with heart failure generally require chronic treatment, although often at lower doses than

Clinical Guideline	Recommendation(s)

	those required initially to achieve diuresis. Decreasing or discontinuing therapy may be considered in patients experiencing significant improvement in clinical status and cardiac function or in those who successfully restrict dietary sodium intake. These patients may undergo cautious weaning of diuretic dose and frequency with careful observation for recurrent fluid retention.
	• Patients and caregivers should be given education on the early signs of fluid retention and the plan for initial therapy.
	• Selected patients may be educated to adjust daily dose of diuretic in response to weight gain from fluid overload.
	
	<u>Evaluation and management of patients with acute decompensated heart failure</u>
	• Patients admitted with acute decompensated heart failure and evidence of fluid overload be treated initially with loop diuretics; usually given intravenously rather than orally. Ultrafiltration may be considered in lieu of diuretics.
	• Diuretics should be administered at doses needed to produce a rate of diuresis sufficient to achieve optimal volume status with relief of signs and symptoms of congestion, without inducing an excessively rapid reduction in intravascular volume or serum electrolytes.
	• Monitoring of daily weights, intake and output is recommended to assess clinical efficacy of diuretic therapy.
	• Careful observation for development of a variety of side effects, including renal dysfunction, electrolyte abnormalities, symptomatic hypotension and gout is recommended in patients treated with diuretics, especially when high doses or combination therapy is used.
	• Careful observation for the development of renal dysfunction is recommended in patients treated with diuretics. Patients with moderate to severe renal dysfunction and evidence of fluid retention should continue to be treated with diuretics. In the presence of severe fluid overload, renal dysfunction may improve with diuresis.
	• When congestion fails to improve in response to diuretic therapy, the following options should be considered:
	  ○ Re-evaluating the presence/absence of congestion.
	  ○ Sodium and fluid restriction.
	  ○ Increasing doses of loop diuretic.
	  ○ Continuous infusion of a loop diuretic.
	  ○ Addition of a second type of diuretic orally (metolazone or spironolactone) or intravenously (chlorothiazide).
	  ○ Ultrafiltration may be considered as well.

European Society of Cardiology: **Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (2016)**[11]	<u>Pharmacological treatments indicated in patients with symptomatic (NYHA Class II-IV) heart failure with reduced ejection fraction</u> • An ACE inhibitor is recommended, in addition to a beat-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death. • A mineralocorticoid receptor antagonist 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. • Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion. • 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. • Ivabradine should be considered to reduce the risk of HF hospitalization or cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm

Clinical Guideline	Recommendation(s)
	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. • 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 heart failure with preserved ejection fraction and heart failure with mid-range ejection fraction</u> • It is recommended to screen patients with HFpEF or HFmrEF (mid-range) 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 or HFmrEF in order to alleviate symptoms and signs. <u>Recommendations for initial management of a rapid ventricular rate in patients with heart failure and atrial fibrillation in the acute or chronic setting</u> • Urgent electrical cardioversion is recommended if AF is thought to be contributing to the patient's hemodynamic compromise in order to improve the patient clinical condition. • For patients in NYHA Class IV, in addition to treatment for acute HF, an intravenous bolus of amiodarone or, in digoxin-naïve patients, an intravenous bolus of digoxin should be considered to reduce the ventricular rate. • For patients in NYHA Class I–III, a β-blocker, usually given orally, is safe and therefore is recommended as first-line treatment to control ventricular rate, provided the patient is euvolemic. • For patients in NYHA Class I–III, digoxin should be considered when ventricular rate remains high despite β-blockers or when β-blockers are not tolerated or contraindicated. • Treatment with dronedarone to improve ventricular rate control is not recommended due to safety concerns. <u>Recommendations for cardiac imaging in patients with suspected or established</u>

Clinical Guideline	Recommendation(s)
	heart failure • Transthoracic Echocardiogram (TTE) is recommended for the assessment of myocardial structure and function in subjects with suspected HF in order to establish a diagnosis of HFrEF, HFmrEF, or HFpEF. • TTE is recommended for the assessment of LVEF in order to identify patients with HF who would be suitable for evidence-based pharmacological and device treatment recommended for HFrEF. Recommendations aiming to prevent or delay the development of overt heart failure or prevent death before the onset of symptoms • Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life. • ACE inhibitor is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction in order to prevent or delay the onset of HF and prolong life. • Beta-blocker is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction, in order to prevent or delay the onset of HF and prolong life. Pharmacological treatments indicated in patients with symptomatic 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 β-blocker is recommended, in addition to an ACE inhibitor, for patients with stable, symptomatic HFrEF to reduce the risk of HF hospitalization and death. • A mineralocorticoid receptor antagonist 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. Other pharmacological treatments recommended in selected patients with symptomatic heart failure with reduced ejection fraction • Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion. • 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. Treatments (or combinations of treatments) that may cause harm in patients with symptomatic (New York Heart Association Class II–IV) heart failure with reduced ejection fraction • Diltiazem or verapamil are not recommended in patients with HFrEF, as they increase the risk of HF worsening and HF hospitalization. • The addition of an ARB (or a renin inhibitor) to the combination of an ACE inhibitor and a mineralocorticoid receptor antagonist is not recommended in patients with HF, because of the increased risk of renal dysfunction and hyperkalemia. Not-recommended treatments of co-morbidities in patients with heart failure • Thiazolidinediones (glitazones) are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization. • NSAIDs or COX-2 inhibitors are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization. Recommendations for the management of patients with acute heart failure –

Clinical Guideline	Recommendation(s)
	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. • In patients with new-onset AHF or those with chronic, decompensated HF not receiving oral diuretics the initial recommended dose should be 20 to 40 mg intravenous furosemide (or equivalent); for those on chronic diuretic therapy, initial intravenous dose should be at least equivalent to oral dose. • It is recommended to give diuretics either as intermittent boluses or a continuous infusion, and the dose and duration should be adjusted according to the patients' symptoms and clinical status. • Inotropic agents are not recommended unless the patient is symptomatically hypotensive or hypoperfused because of safety concern.
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, 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.
American Society of Hypertension/ International Society of	Nonpharmacologic treatment • In patients with hypertension that is no more severe than stage one and is not associated with evidence of abnormal cardiovascular findings or other

Clinical Guideline	Recommendation(s)

Hypertension: **Clinical Practice Guidelines for the Management of Hypertension in the Community (2014)**[13]	cardiovascular risks, six to 12 months of lifestyle changes can be attempted in the hope that they may be sufficiently effective to make it unnecessary to use medicines.
	• It may be prudent to start treatment with drugs sooner if it is clear that the blood pressure is not responding to the lifestyle methods or if other risk factors appear.
	• Weight loss: In patients who are overweight or obese, weight loss is helpful in treating hypertension, diabetes, and lipid disorders.
	• Salt reduction: Reduction of salt intake is recommended because it can reduce blood pressure and decrease the need for medications in patients who are "salt sensitive."
	• Exercise: Regular aerobic exercise can help reduce blood pressure.
	• Alcohol consumption: Up to two drinks a day can be helpful in protecting against cardiovascular events, but greater amounts of alcohol can raise blood pressure and should therefore be discouraged. In women, alcohol should be limited to one drink a day.
	• Cigarette smoking: Stopping smoking will not reduce blood pressure, but since smoking by itself is such a major cardiovascular risk factor, patients must be strongly urged to discontinue this habit.
	
	<u>Drug treatment of hypertension</u>
	• Treatment with drugs should be started in patients with blood pressures >140/90 mm Hg in whom lifestyle treatments have not been effective.
	• In patients with stage two hypertension (blood pressure ≥160/100 mm Hg), drug treatment should be started immediately after diagnosis, usually with a two-drug combination, without waiting to see the effects of lifestyle changes.
	• For patients older than 80 years, the suggested threshold for starting treatment is at levels ≥150/90 mm Hg. Thus, the target of treatment should be <140/90 mm Hg for most patients but <150/90 mm Hg for older patients (unless these patients have chronic kidney disease or diabetes, when <140/90 mm Hg can be considered).
	• Most patients will require more than one drug to achieve control of their blood pressure.
	• In general, increase the dose of drugs or add new drugs at approximately two to three week intervals. This frequency can be faster or slower depending on the judgment of the practitioner. In general, the initial doses of drugs chosen should be at least half of the maximum dose so that only one dose adjustment is required thereafter. It is generally anticipated that most patients should reach an effective treatment regimen, whether one, two, or three drugs, within six to eight weeks.
	• Choice of drugs should be influenced by the age, ethnicity/race, and other clinical characteristics of the patient.
	• The choice of drugs will also be influenced by other conditions (e.g., diabetes and coronary disease) associated with the hypertension. Pregnancy also influences drug choice.
	• Long-acting drugs that need to be taken only once daily are preferred to shorter-acting drugs that require multiple doses because patients are more likely to follow a simple treatment regimen.
	• This guideline only makes recommendations for drug classes, not individual agents. There is an assumption, unless otherwise stated, that all drugs in a class are similar to each other.
	• Drug selectin when hypertension is the only or main concern:
	  ○ For black patients of all ages, use calcium channel blocker (CCB) or thiazide diuretic as first drug, then add angiotensin receptor blocker (ARB) or angiotensin-converting enzyme (ACE) inhibitor if needed.
	  ○ For white and other non-black patients <60 years of age, use ARB or ACE

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	inhibitor as first drug, then add CCB or thiazide diuretic if needed. ○ For white and other non-black patients ≥60 years of age, use CCB or thiazide diuretic as first drug, then add ARB or ACE inhibitor if needed. • Drug selection when hypertension is associated with other conditions: ○ For patients with hypertension and diabetes, use ARB or ACE inhibitor as first drug (note, in black patients it is acceptable to start with a CCB or thiazide), then add CCB or thiazide diuretic (unless starting on CCB or thiazide in black patients) if needed. ○ For patients with hypertension and chronic kidney disease, use ARB or ACE inhibitor as first drug, then add CCB or thiazide diuretic if needed. ○ For patients with hypertension and clinical coronary artery disease, use β-blocker plus ARB or ACE inhibitor as first drugs, then add CCB or thiazide diuretic if needed. ○ For patients with hypertension and stroke history, use ACE inhibitor or ARB as first drug, then add thiazide diuretic or CCB if needed. • For patients with hypertension and heart failure, patients with h symptomatic heart failure should usually receive an ARB or ACE inhibitor plus β-blocker plus diuretic plus spironolactone regardless of blood pressure. A dihydropyridine CCB can be added if needed for blood pressure control.
Hypertension Canada: **2017 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults (2017)**[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. <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.

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	• 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. Guidelines for individuals 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

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	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.
	
	<u>Treatment of hypertension in association with stroke</u>
	• BP management in acute ischemic stroke (onset to 72 hours)
	  ○ For patients with ischemic stroke not eligible for thrombolytic therapy, treatment of hypertension in the setting of acute ischemic stroke or transient ischemic attack should not be routinely undertaken. Extreme BP increases (e.g., SBP >220 mmHg or DBP >120 mmHg) may be treated to reduce the BP by approximately 15%, and not more than 25%, over the first 24 hours with gradual reduction thereafter. Avoid excessive lowering of BP because this might exacerbate existing ischemia or might induce ischemia, particularly in the setting of intracranial arterial occlusion or extracranial carotid or vertebral artery occlusion. Pharmacological agents and routes of administration should be chosen to avoid precipitous decreases in BP.
	  ○ For patients with ischemic stroke eligible for thrombolytic therapy, very high BP (>185/110 mmHg) should be treated concurrently in patients receiving thrombolytic therapy for acute ischemic stroke to reduce the risk of secondary intracranial hemorrhage.
	• 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)
	  ○ For patients with intracerebral hemorrhage (ICH) in the hyperacute phase (in the first 24 hours) SBP lowering to <140 mmHg should be avoided because of an absence of benefit (relative to a target of <180 mmHg) and some suggestion of harm.
	
	<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,

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	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 • For patients with nondiabetic chronic kidney disease, target BP is <140/90 mmHg. • For patients with hypertension and proteinuric chronic kidney disease (urinary protein >500 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. • Thiazide/thiazide-like diuretics are recommended as additive antihypertensive therapy. For patients with chronic kidney disease and volume overload, loop diuretics are an alternative. • 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. • In patients with hypertension attributable to FMD-related renal artery stenosis, revascularization should be considered. • 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 2 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. Combination therapy using two first-line agents may also be considered as initial treatment of hypertension if SBP is 20 mmHg greater than target or if DBP is 10 mmHg greater than target. However, caution should be exercised in patients in whom a substantial decrease in BP is more likely or poorly tolerated (e.g., elderly patients and patients with autonomic neuropathy). • 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.

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European Society of Hypertension/European Society of Cardiology: **2013 Guidelines for the management of arterial hypertension (2013)**[15]	The 2013 guidelines on hypertension of the European Society of Hypertension and the European Society of Cardiology follow the guidelines jointly issued by the two societies in 2003 and 2007. <u>Treatment strategies and choice of antihypertensive drugs</u> • Diuretics (including thiazides, chlorthalidone, and indapamide), β-blockers, calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) are all suitable for the initiation and maintenance of antihypertensive treatment, either as monotherapy or in some combinations. • Some agents should be considered as the preferential choice in specific conditions because used in trials in those conditions or because of greater effectiveness in specific types of organ damage. • Initiation of antihypertensive therapy with a two-drug combination may be considered in patients with markedly high baseline blood pressure (BP) or at high cardiovascular (CV) risk. • The combination of two antagonists of the renin-angiotensin system (RAS) is not recommended and should be discouraged. • Other drug combinations should be considered and probably are beneficial in proportion to the extent of BP reduction. However, combinations that have been successfully used in trials may be preferable. • Combinations of two antihypertensive drugs at fixed doses in a single tablet may be recommended and favored, because reducing the number of daily pills improves adherence, which is low in patients with hypertension. <u>Treatment strategies in white-coat and masked hypertension</u> • In white-coat hypertensives without additional risk factors, therapeutic intervention may be limited to lifestyle changes only, but this decision should be accompanied by close follow-up. • In white-coat hypertensives with a higher CV risk because of metabolic derangements or asymptomatic organ damage, drug treatment may be considered in addition to lifestyle changes. • In masked hypertension, both lifestyle measures and antihypertensive drug treatment should be considered, because this type of hypertension has been consistently found to have a CV risk very close to that of in- and out-of-office hypertension. <u>Antihypertensive treatment strategies in the elderly</u> • In elderly hypertensives with SBP ≥160 mmHg there is solid evidence to recommend reducing SBP to between 150 and 140 mmHg. • In fit elderly patients <80 years old antihypertensive treatment may be considered at SBP values ≥140 mmHg with a target SBP <140 mmHg if treatment is well tolerated. • In individuals older than 80 years with an initial SBP ≥160 mmHg, it is recommended to reduce SBP to between 150 and 140 mmHg, provided they are in good physical and mental conditions. • In frail elderly patients, it is recommended to leave decisions on antihypertensive therapy to the treating physician, and based on monitoring of the clinical effects of treatment. • Continuation of well-tolerated antihypertensive treatment should be considered when a treated individual becomes an octogenarian. • All hypertensive agents are recommended and can be used in the elderly, although diuretics and calcium antagonists may be preferred in isolated systolic hypertension.

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	Treatment strategies in hypertensive women • Hormone therapy and selective estrogen receptor modulators are not recommended and should not be used for primary or secondary prevention of CVD. • If treatment of younger perimenopausal women is considered for severe menopausal symptoms, the benefits should be weighed against potential risks. • Drug treatment of severe hypertension in pregnancy (SBP >160 mmHg or DBP >110 mmHg) is recommended. • Drug treatment may also be considered in pregnant women with persistent elevation of BP ≥150/95 mmHg, and in those with BP ≥140/90 mmHg in the presence of gestational hypertension, subclinical organ damage or symptoms. • In women at high risk of pre-eclampsia, provided they are at low risk of gastrointestinal hemorrhage, treatment with low dose aspirin from 12 weeks until delivery may be considered. • In women with child-bearing potential RAS blockers are not recommended and should be avoided. • Methyldopa, labetalol, and nifedipine should be considered preferential antihypertensive drugs in pregnancy. Intravenous labetalol or infusion of nitroprusside should be considered in case of emergency (pre-eclampsia). Treatment strategies in patients with diabetes • While initiation of antihypertensive drug treatment in diabetic patients whose SBP is ≥160 mmHg is mandatory, it is strongly recommended to start drug treatment also when SBP is ≥140 mmHg. • A SBP goal <140 mmHg is recommended in patients with diabetes. • The DBP target in patients with diabetes is recommended to be <85 mmHg. • All classes of antihypertensive agents are recommended and can be used in patients with diabetes; RAS blockers may be preferred, especially in the presence of proteinuria or microalbuminuria. • It is recommended that individual drug choice takes comorbidities into account. • Simultaneous administration of two blockers of the RAS is not recommended and should be avoided in patients with diabetes Treatment strategies in hypertensive patients with metabolic syndrome • Lifestyle changes, particularly weight loss and physical exercise, are to be recommended to all individuals with the metabolic syndrome. These interventions improve not only BP, but the metabolic components of the syndrome and delay diabetes onset. • As the metabolic syndrome can be considered a 'pre-diabetic' state, antihypertensive agents potentially improving or at least not worsening insulin sensitivity, such as RAS blockers and calcium antagonists, should be considered as the preferred drugs. Beta-blockers (with the exception of vasodilating β-blockers) and diuretics should be considered only as additional drugs, preferably in association with a potassium-sparing agent. • It is recommended to prescribe antihypertensive drugs with particular care in hypertensive patients with metabolic disturbances when BP is ≥140/90 mmHg after a suitable period of lifestyle changes, and to maintain BP <140/90 mmHg. • BP lowering drugs are not recommended in individuals with metabolic syndrome and high normal BP. Therapeutic strategies in hypertensive patients with nephropathy • Lowering SBP to <140 mmHg should be considered. • When overt proteinuria is present, SBP values <130 mmHg may be considered, provided that changes in eGFR are monitored. • RAS blockers are more effective in reducing albuminuria than other

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	antihypertensive agents, and are indicated in hypertensive patients in the presence of microalbuminuria or overt proteinuria. • Reaching BP goals usually requires combination therapy, and it is recommended to combine RAS blockers with other antihypertensive agents. • Combination of two RAS blockers, though potentially more effective in reducing proteinuria, is not recommended. • Aldosterone antagonists cannot be recommended in chronic kidney disease (CKD), especially in combination with a RAS blocker, because of the risk of excessive reduction in renal function and of hyperkalemia. <u>Therapeutic strategies in hypertensive patients with cerebrovascular disease</u> • It is not recommended to intervene with BP-lowering therapy during the first week after acute stroke irrespective of BP level, although clinical judgement should be used in the face of very high SBP values. • Antihypertensive treatment is recommended in hypertensive patients with a history of stroke or transient ischemic attack (TIA), even when initial SBP is in the 140 to 159 mmHg range. • In hypertensive patients with a history of stroke or TIA, a SBP goal of <140 mmHg should be considered. • In elderly hypertensives with previous stroke or TIA, SBP values for intervention and goal may be considered to be somewhat higher. • All drug regimens are recommended for stroke prevention, provided that BP is effectively reduced. <u>Therapeutic strategies in hypertensive patients with heart disease</u> • In hypertensive patients with CHD, a SBP goal <140 mmHg should be considered. • In hypertensive patients with a recent myocardial infarction, β-blockers are recommended. In case of other CHD all antihypertensive agents can be used, but β-blockers and calcium antagonists are to be preferred for symptomatic reasons (angina). • Diuretics, β-blockers, ACE inhibitors, angiotensin receptor blockers, and/or mineralocorticoid receptor antagonists are recommended in patients with heart failure or severe left ventricular (LV) dysfunction to reduce mortality and hospitalization. • In patients with heart failure and preserved ejection fraction (EF), there is no evidence that antihypertensive therapy per se or any particular drug is beneficial. However, in these patients, as well as in patients with hypertension and systolic dysfunction, lowering SBP to around 140 mmHg should be considered. Treatment guided by relief of symptoms (congestion with diuretics, high heart rate with β-blockers, etc.) should also be considered. • ACE inhibitors and angiotensin receptor blockers (and β-blockers and mineralocorticoid receptor antagonists if heart failure coexists) should be considered as antihypertensive agents in patients at risk of new or recurrent atrial fibrillation. • It is recommended that all patients with left ventricular hypertrophy (LVH) receive antihypertensive agents. • In patients with LVH, initiation of treatment with one of the agents that have shown a greater ability to regress LVH should be considered, i.e. ACE inhibitors, angiotensin receptor blockers, and calcium antagonists. <u>Therapeutic strategies in hypertensive patients with atherosclerosis, arteriosclerosis, and peripheral artery disease (PAD)</u> • In the presence of carotid atherosclerosis, prescription of calcium antagonists and ACE inhibitors should be considered as these agents have shown a greater

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	efficacy in delaying atherosclerosis progression than diuretics and β-blockers. • In hypertensive patients with a pulse wave velocity above 10 m/s, all antihypertensive drugs should be considered provided that a BP reduction to <140/90 mmHg is consistently achieved. • Antihypertensive therapy is recommended in hypertensive patients with PAD to achieve a goal of <140/90 mmHg, because of their high risk of myocardial infarction, stroke, heart failure, and CV death. • Though a careful follow up is necessary, β-blockers may be considered for the treatment of arterial hypertension in patients with PAD, since their use does not appear to be associated with exacerbation of PAD symptoms.

National Institute for Health and Clinical Excellence: **Hypertension in adults: diagnosis and management (2011)**[16]
 	
Reaffirmed Nov 2016
	Choosing antihypertensive drug treatment
	• 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 people ≥80 years of age the same antihypertensive drug treatment as people aged 55 to 80 years, taking into account any comorbidities.
	• Offer antihypertensive drug treatment to women of child-bearing potential in line with the recommendations on Management of pregnancy with chronic hypertension and Breastfeeding in 'Hypertension in pregnancy' (NICE clinical guideline 107).
	
	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). 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 step one antihypertensive (ACE inhibitor, ARB) with a calcium channel blocker (CCB) to patients >55 years of age and to black patients of African or Caribbean family origin 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 chlorthalidone (12.5 to 25.0 mg once daily) or indapamide (1.5 mg modified-release once daily or 2.5 mg once daily) in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide.
	• For patients who are already receiving treatment with bendroflumethiazide or hydrochlorothiazide and whose blood pressure is stable and well controlled, continue treatment as is.
	• β-blockers are not a preferred initial therapy for hypertension; however, β-blockers may be considered in younger patients, particularly:
	  ○ Patients with an intolerance or contraindication to ACE inhibitors and ARBs.
	  ○ Women of child-bearing potential.
	  ○ People with evidence of increased sympathetic drive.
	• If treatment is initiated with a β-blocker and a second antihypertensive is required, add a CCB over a thiazide-like diuretic to reduce the risk of developing diabetes.
	
	Step two treatment
	• If blood pressure is not controlled with a step one antihypertensive, offer a step two treatment with a CCB in combination with an ACE inhibitor or an ARB.

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	• If a CCB is not appropriate or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic.
	• For black patients of African or Caribbean family origin, consider an ARB in preference to an ACE inhibitor, in combination with a CCB.
	
	Step three treatment
	• Before considering step three treatment, review medication to ensure step two treatment is at optimal or best tolerated doses.
	• If three drugs are required to control blood pressure, the combination of an ACE inhibitor or ARB, CCB, and thiazide-like diuretic should be utilized.
	
	Step four treatment
	• Regard clinic blood pressure that remains >140/90 mmHg after treatment with the optimal or best tolerated doses of an ACE inhibitor or an ARB plus a CCB plus a diuretic as resistant hypertension, and consider adding a fourth antihypertensive drug and/or seeking expert advice.
	• For treatment of resistant hypertension at step four:
	  ○ Consider further diuretic therapy with low-dose spironolactone (25 mg once daily) if the blood potassium level is 4.5 mmol/l or lower. Use particular caution in people with a reduced estimated glomerular filtration rate because they have an increased risk of hyperkalemia.
	  ○ Consider higher-dose thiazide-like diuretic treatment if the blood potassium level is higher than 4.5 mmol/l.
	  ○ If further diuretic therapy for resistant hypertension is not tolerated or is contraindicated or ineffective, consider an α-blocker or β-blocker.

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. • 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 management in chronic kidney disease (CKD) non-dialysis (ND) patients without diabetes mellitus • The Work Group recommends that non-diabetic adults with CKD ND and urine albumin excretion <30 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >140 mm Hg systolic or >90 mm Hg diastolic be treated with blood pressure -lowering drugs to maintain a blood pressure that is

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Blood Pressure in Chronic Kidney Disease (2012)[18]	consistently ≤140 mm Hg systolic and ≤90 mm Hg diastolic. • The Work Group suggests that non-diabetic adults with CKD ND and urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with BP-lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic. • The Work Group suggests that non-diabetic adults with CKD ND and urine albumin excretion >300 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with blood pressure -lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤ 80 mm Hg diastolic. • The Work Group suggests that an angiotensin receptor blocker (ARB) or angiotensin converting enzyme inhibitor (ACE-I) be used in non-diabetic adults with CKD ND and urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*) in whom treatment with blood pressure -lowering drugs is indicated. • The Work Group recommends that an ARB or ACE-I be used in non-diabetic adults with CKD ND and urine albumin excretion >300 mg per 24 hours (or equivalent*) in whom treatment with blood pressure -lowering drugs is indicated. <u>Blood pressure management in CKD ND patients with diabetes mellitus</u> • The Work Group recommends that adults with diabetes and CKD ND with urine albumin excretion <30 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >140 mm Hg systolic or >90 mm Hg diastolic be treated with BP-lowering drugs to maintain a blood pressure that is consistently ≤140 mm Hg systolic and ≤90 mm Hg diastolic. • The Work Group suggests that adults with diabetes and CKD ND with urine albumin excretion >30 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with BP-lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic. • The Work Group suggests that an ARB or ACE-I be used in adults with diabetes and CKD ND with urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*). • The Work Group recommends that an ARB or ACE-I be used in adults with diabetes and CKD ND with urine albumin excretion >300 mg per 24 hours (or equivalent*). <u>Blood pressure management in kidney transplant recipients (non–dialysis-dependent CKD of any stage with a kidney transplant [CKD T])</u> • The Work Group suggests that adult kidney transplant recipients whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic, irrespective of the level of urine albumin excretion. • In adult kidney transplant recipients, choose a blood pressure -lowering agent after taking into account the time after transplantation, use of calcineurin inhibitors, presence or absence of persistent albuminuria, and other co morbid conditions. <u>Blood pressure management in children with CKD ND</u> • The Work Group recommends that in children with CKD ND, blood pressure -lowering treatment is started when blood pressure is consistently above the 90th percentile for age, sex, and height. • The Work Group suggests that in children with CKD ND (particularly those

Clinical Guideline	Recommendation(s)
	with proteinuria), blood pressure is lowered to consistently achieve systolic and diastolic readings less than or equal to the 50th percentile for age, sex, and height, unless achieving these targets is limited by signs or symptoms of hypotension. • The Work Group suggests that an ARB or ACE-I be used in children with CKD ND in whom treatment with blood pressure -lowering drugs is indicated, irrespective of the level of proteinuria. Blood pressure management in elderly persons with CKD ND • Tailor blood pressure treatment regimens in elderly patients with CKD ND by carefully considering age, co-morbidities and other therapies, with gradual escalation of treatment and close attention to adverse events related to blood pressure treatment, including electrolyte disorders, acute deterioration in kidney function, orthostatic hypotension and drug side effects. *Approximate equivalents for albumin excretion rate per 24 hours is expressed as protein excretion rate per 24 hours, albumin/creatinine ratio, protein/creatinine ratio, and protein reagent strip results.
American Diabetes Association: **Standards of Medical Care in Diabetes (2017)**[19]	Hypertension/blood pressure control • Blood pressure should be measured at every routine visit. Patients found to have elevated blood pressure should have blood pressure confirmed on a separate day. • Most patients with diabetes and hypertension should be treated to a systolic blood pressure goal of <140 mmHg and a diastolic blood pressure goal of <90 mmHg. • Lower systolic and diastolic blood pressure targets, such as 130/80 mmHg, may be appropriate for individuals at high risk of cardiovascular disease, if they can be achieved without undue treatment burden. • In pregnant patients with diabetes and chronic hypertension, blood pressure targets of 120 to 160/80 to 105 mmHg are suggested in the interest of optimizing long-term maternal health and minimizing impaired fetal growth. • Patients with confirmed office-based blood pressure >140/90 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). 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. • For patients with blood pressure >120/80 mmHg, lifestyle intervention consists of weight loss if overweight or obese; a Dietary Approaches to Stop Hypertension–style dietary pattern including reducing sodium and increasing

Clinical Guideline	Recommendation(s)
	potassium intake; moderation of alcohol intake; and increased physical activity. Coronary heart disease • In asymptomatic patients, routine screening for coronary artery disease is not recommended as it does not improve outcomes as long as atherosclerotic cardiovascular disease risk factors are treated. • Consider investigations for coronary artery disease in the presence of any of the following: atypical cardiac symptoms (e.g., unexplained dyspnea, chest discomfort); signs or symptoms of associated vascular disease including carotid bruits, transient ischemic attack, stroke, claudication, or peripheral arterial disease; or electrocardiogram abnormalities (e.g., Q waves). • In patients with known atherosclerotic cardiovascular disease, use aspirin and statin therapy (if not contraindicated) and consider ACE inhibitor therapy to reduce the risk of cardiovascular events. • In patients with prior myocardial infarction, β-blockers should be continued for at least two years after the event. • In patients with symptomatic heart failure, thiazolidinedione treatment should not be used. • In patients with type 2 diabetes with stable congestive heart failure, metformin may be used if estimated glomerular filtration remains >30 mL/min but should be avoided in unstable or hospitalized patients with congestive heart failure. Diabetic 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, in all patients with type 2 diabetes, and in all patients with comorbid hypertension. • Optimize glucose control to reduce the risk or slow the progression of diabetic kidney disease. • Optimize blood pressure control to reduce the risk or slow the progression of diabetic kidney disease. • For people with nondialysis-dependent diabetic kidney disease, dietary protein intake should be approximately 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. • 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) B 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 or changes in potassium when ACE inhibitors, angiotensin receptor blockers, or diuretics are used. • Continued monitoring of urinary albumin–to–creatinine ratio in patients with albuminuria treated with an ACE inhibitor or an angiotensin receptor blocker is reasonable to assess the response to treatment and progression of diabetic kidney disease. • An ACE inhibitor or an angiotensin receptor blocker is not recommended for the primary prevention of diabetic kidney disease 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. • When estimated glomerular filtration rate is <60 mL/min/1.73 m^2, evaluate and manage potential complications of chronic kidney disease. • Patients should be referred for evaluation for renal replacement treatment if they

Clinical Guideline	Recommendation(s)
	have an estimated glomerular filtration rate <30 mL/min/1.73 m^2. • Promptly refer to a physician experienced in the care of kidney disease 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[1-4]

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 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.
†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[6]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Amiloride	30 to 90	Not significant	Not metabolized	Feces (40 to 50)	6 to 9

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
		(% not reported)		Renal (50)	
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[6]

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 (amiloride, triamterene)	ACE inhibitors	Hyperkalemia, possibly with cardiac arrhythmias or arrest may occur with the combination of amiloride and ACE 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	Digitalis glycosides	Diuretic-induced electrolyte disturbances may predispose

Generic Name(s)	Interaction	Mechanism
(HCTZ)		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[1-6]

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
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	-

Adverse Events	Single Entity Agents		Combination Products	
	Amiloride	Triamterene	Amiloride And HCTZ	Triamterene and HCTZ
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				
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[5]

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 and Triamterene-Hydrochlorothiazide[5]

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 and Hydrochlorothaizide[5]

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[1-6]

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 50-25 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.[20] (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.[21] (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.[22] (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.[23] (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.[24] (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.[25] (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.[26] (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[27] (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.[28] (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.[29] (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.[30] (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.[31] (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.[32] (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.[33] (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.[34] (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.[35]	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.[36] (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.[37] (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.[38] (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.[39] (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	$$
Triamterene	capsule	Dyrenium®	$$$$$	N/A
Combination Products				
Amiloride and HCTZ	tablet	N/A	N/A	$
Triamterene and HCTZ	capsule, tablet	Dyazide®*, Maxzide®*	$$$	$

*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.[1-4] 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.[1-4] Amiloride and triamterene are available as a fixed-dose combination with hydrochlorothiazide. All of the products with the exception of triamterene 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.[9-11] 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.[1-4] Triamterene may be used along or with other diuretics, either for its added diuretic effect or its potassium-sparing potential.[3]

There are several national and international organizations that have published guidelines on the treatment of hypertension.[12-19] 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).[12] Several guidelines consistently recommend that the selection of an antihypertensive agent be based on compelling indications for use.[12-19] Most patients will require more than one antihypertensive medication to achieve blood pressure goals.[12-19] The use of a fixed-dose combination product may simplify the treatment regimen and improve adherence.[14,15,18] 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, 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.[20-39]

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
November 8, 2017

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.[1-5] 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.[4-6]

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 August 2015.

Table 1. Thiazide Diuretics Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Chlorothiazide	injection*, suspension, tablet*	Diuril®	chlorothiazide
Hydrochlorothiazide	capsule, tablet	Microzide®*	hydrochlorothiazide
Methyclothiazide	tablet	N/A	methyclothiazide

*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 College of Cardiology/American Heart Association: **Guideline for the Management of Heart Failure (2013)**[7]	<u>Treatment of Stage A heart failure (HF)</u> • Hypertension and lipid disorders should be controlled in accordance with guidelines to lower the risk of HF. (Level of Evidence (LoE): A) • Other conditions that may lead to or contribute to HF, such as obesity, diabetes mellitus, tobacco use, and known cardiotoxic agents, should be controlled or avoided. (LoE: C) <u>Treatment of Stage B heart failure</u> • In patients with a history of MI and reduced EF, ACE inhibitors or ARBs should be used to prevent HF. (LoE: A) • In patients with MI and reduced EF, evidence-based β-blockers (using one of three proven to reduce mortality [i.e., bisoprolol, carvedilol, and sustained-release metoprolol succinate]) should be used to prevent HF. (LoE: B) • In patients with MI, statins should be used to prevent HF. (LoE: A) • ACE inhibitors and β-blockers should be used in all patients with a reduced EF to prevent symptomatic HF, even if they do not have a history of MI. (LoE: A and C, respectively)

Clinical Guideline	Recommendation(s)
	• Blood pressure should be controlled to prevent symptomatic HF. (LoE: A) • Nondihydropyridine calcium channel blockers may be harmful in patients with low LVEF. (LoE: C) <u>Pharmacological treatment for Stage C HFrEF</u> • Recommendations for patients in Stages A and B are recommended where appropriate for patients in Stage C. (LoE: A, B, and C as appropriate) • Diuretics are recommended in patients with HFrEF who have evidence of fluid retention, unless contraindicated, to improve symptoms. (LoE: C) • ACE inhibitors are recommended in patients with HFrEF and current or prior symptoms, unless contraindicated, to reduce morbidity and mortality. ARBs are recommended as alternative therapy in ACE inhibitor intolerant patients. (LoE: A) • Use of one of the three β-blockers proven to reduce mortality is recommended for all patients with current or prior symptoms of HFrEF, unless contraindicated, to reduce morbidity and mortality. (LoE: A) • Aldosterone receptor antagonists are recommended in patients with NYHA class II–IV HF and who have LVEF of ≤35%, unless contraindicated, to reduce morbidity and mortality. Patients with NYHA class II HF should have a history of prior cardiovascular hospitalization or elevated plasma natriuretic peptide levels to be considered for aldosterone receptor antagonists. Creatinine should be ≤2.5 mg/dL in men or ≤2.0 mg/dL in women (or estimated glomerular filtration rate >30 mL/min/1.73 m^2), and potassium should be <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) • The combination of hydralazine and isosorbide dinitrate is recommended to reduce morbidity and mortality for patients self-described as African Americans with NYHA class III–IV HFrEF receiving optimal therapy with ACE inhibitors and β-blockers, unless contraindicated. (LoE: A) • Digoxin can be beneficial in patients with HFrEF, unless contraindicated, to decrease hospitalizations for HF. (LoE: B) • Patients with chronic HF with permanent/persistent/paroxysmal AF and an additional risk factor for cardioembolic stroke (history of hypertension, diabetes mellitus, previous stroke or transient ischemic attack, or ≥75 years of age) should receive chronic anticoagulant therapy. (LoE: A) • Statins are not beneficial as adjunctive therapy when prescribed solely for the diagnosis of HF in the absence of other indications for their use. (LoE: A) • Calcium channel blockers are not recommended as routine treatment for patients with HFrEF. (LoE: A) <u>Pharmacological treatment for Stage C HFpEF</u> • Blood pressure should be controlled according to published clinical practice guidelines. (LoE: B) • Diuretics should be used for relief of symptoms due to volume overload. (LoE: C) • The use of β-blocking agents, ACE inhibitors, and ARBs in patients with hypertension is reasonable to control blood pressure in patients with HFpEF. (LoE: C) <u>Treatment of Stage D (advanced/refractory) HF</u> • Fluid restriction (1.5 to 2 L/d) is reasonable, especially in patients with hyponatremia, to reduce congestive symptoms. (LoE: C) • Until definitive therapy (e.g., coronary revascularization, mechanical circulatory support, heart transplantation) or resolution of the acute precipitating problem, patients with cardiogenic shock should receive temporary intravenous inotropic support to maintain systemic perfusion and preserve end-organ performance.

Clinical Guideline	Recommendation(s)
	(LoE: C) • Continuous intravenous inotropic support is reasonable as "bridge therapy" in patients with stage D HF refractory to medical therapy and device therapy who are eligible for and awaiting mechanical circulatory support or cardiac transplantation. (LoE: B) • Long-term use of either continuous or intermittent, intravenous parenteral positive inotropic agents, in the absence of specific indications or for reasons other than palliative care, is potentially harmful in the patient with HF. (LoE: B)
Heart Failure Society of America: **Heart Failure Society of America 2010 Comprehensive Heart Failure Practice Guidelines (Executive Summary) (2010)[8]**	<u>Patients with left ventricular systolic dysfunction</u> • ACE inhibitors should be used in all patients with a LVEF ≤40%, unless otherwise contraindicated. • ARBs may be used in patients who are intolerant to ACE inhibitors. Hydralazine and a nitrate may be used in patients intolerant to ACE inhibitors and ARBs, or in whom such therapy is contraindicated. • The combination of an ACE inhibitor and a β-blocker is recommended in all patients with a LVEF ≤40%. • The routine use of an ARB with a combination of an ACE inhibitor and β-blocker in patients who have had a MI and have left ventricular dysfunction is not recommended. • The addition of an ARB can be considered in patients with heart failure due to reduced LVEF who have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor and a β-blocker. • Individual ARBs may be considered as initial therapy (instead of an ACE inhibitor) in patients with heart failure who have had a MI and in patients with chronic heart failure and systolic dysfunction. • ARBs are recommended in patients who cannot tolerate ACE inhibitors due to cough. The combination of hydralazine and an oral nitrate may be considered in such patients not tolerating ARB therapy. • Patients intolerant to ACE inhibitors from hyperkalemia or renal insufficiency are likely to experience the same side effects with ARBs. In these cases, the combination of hydralazine and an oral nitrate should be considered. • ARBs should be considered in patients experiencing angioedema while on ACE inhibitors based on their underlying risk and with recognition that angioedema has been reported infrequently with ARBs. The combination of hydralazine and oral nitrates may be considered in such patients not tolerating ARB therapy. • A combination of hydralazine and an oral nitrate is recommended in African American patients with heart failure and reduced left ventricular ejection fraction (LVEF) who are on a standard regimen of an ACE inhibitor (or ARB) and a β-blocker. • A combination of hydralazine and an oral nitrate may be considered in non–African American patients with heart failure and reduced LVEF who are symptomatic despite optimization of standard therapy. • Administration of an aldosterone antagonist is recommended for patients with New York Heart Association (NYHA) class IV (or class III, previously class IV) heart failure from reduced LVEF (<35%) while receiving standard therapy, including diuretics. • Administration of an aldosterone antagonist should be considered in patients following an acute MI, with clinical heart failure signs and symptoms or history of diabetes mellitus, and an LVEF <40%. Patients should be on standard therapy, including an ACE inhibitor (or ARB) and a β-blocker. • The triple combination of an ACE inhibitor, an ARB, and an aldosterone antagonist is not recommended because of the high risk of hyperkalemia. <u>Patients with hypertension and symptomatic left ventricular dysfunction with left ventricular dilation and low LVEF</u>

Clinical Guideline	Recommendation(s)
	• ACE inhibitors, ARBs, β-blockers, aldosterone inhibitors, and isosorbide dinitrate/hydralazine in various combinations (with a loop diuretic if needed) are recommended. • If blood pressure remains >130/80 mm Hg, a dihydropyridine calcium channel blocker (e.g., amlodipine or felodipine) may be considered or other antihypertensive medication doses increased. <u>Managing heart failure in special populations</u> • The combination of hydralazine/isosorbide dinitrate is recommended for African American women with moderate to severe heart failure symptoms who are on background neurohormonal inhibition. • A combination of hydralazine and isosorbide dinitrate is recommended as part of standard therapy in addition to β-blockers and ACE-inhibitors for African Americans with left ventricular systolic dysfunction and NYHA class II-IV heart failure. • As in all patients, but especially in the elderly, careful attention to volume status, the possibility of symptomatic cerebrovascular disease and the presence of postural hypotension are recommended during therapy with ACE inhibitors, β-blockers and diuretics. <u>Patients with heart failure and preserved LVEF</u> • ACE inhibitors or ARBs should be considered in this patient population. • ACE inhibitors should be considered in patients with heart failure and symptomatic atherosclerotic cardiovascular disease or diabetes and at least one other risk factor. ARBs may be used in patients who are intolerant to ACE inhibitors. • Beta-blocker treatment is recommended in patients with HF and preserved LVEF who have prior MI, hypertension, or AF. • Calcium channel blockers should be considered in patients with heart failure and preserved LVEF who have atrial fibrillation requiring ventricular rate control and intolerance to β-blockers (consider diltiazem or verapamil), symptom-limiting angina, or hypertension. • Diuretic therapy is recommended in all patients with heart failure and clinical evidence of volume overload, including those with preserved LVEF. • Treatment may begin with either a thiazide or loop diuretic. In more severe volume overload or if response to a thiazide is inadequate, treatment with a loop diuretic should be implemented. • Excessive diuresis, which may lead to orthostatic changes in blood pressure and worsening renal function, should be avoided. <u>Patients with heart failure and CAD</u> • Calcium channel blockers should be considered in patients who have angina despite optimization of β-blocker and nitrates. Amlodipine and felodipine are preferred in patients with decreased systolic function. <u>Patients with heart failure and hypertension</u> • Patients with left ventricular hypertrophy or left ventricular dysfunction without left ventricular dilation should be treated to a goal blood pressure of <130/80 mm Hg. Treatment with several drugs may be necessary, including an ACE inhibitor (or ARB), a diuretic and a β-blocker or calcium channel blocker. • Patients with asymptomatic left ventricular dysfunction and left ventricular dilation and a reduced ejection fraction should receive an ACE inhibitor and a β-blocker. If blood pressure remains elevated (>130/80 mm Hg), the addition of a diuretic is recommended, followed by a calcium channel blocker or other antihypertensive agent.

Clinical Guideline	Recommendation(s)
	• If blood pressure remains >130/80 mm Hg, then the addition of a thiazide diuretic is recommended, followed by a dihydropyridine calcium channel blocker (e.g., amlodipine or felodipine) or other antihypertensive drugs. <u>Patients at risk for development of heart failure</u> • ACE inhibitors are recommended in patients who are at risk for the development of heart failure including patients with CAD, peripheral vascular disease, stroke, diabetes and another major risk factor, and patients with diabetes who smoke and have microalbuminuria. <u>Patients with asymptomatic heart failure and reduced LVEF</u> • ACE inhibitors are recommended in asymptomatic patients with reduced LVEF (<40%). • ARBs may be used in patients who are intolerant to ACE inhibitors. • Routine use of a combination of ACE inhibitors and ARBs is not recommended. • β-blocker therapy should be considered. <u>Patients with heart failure and ischemic heart disease</u> • ACE inhibitor therapy is recommended in all patients with either reduced or preserved LVEF after a MI. • Beta-blockers are recommended for the management of all patients with reduced LVEF or post-MI. • ACE inhibitor and β-blocker therapy should be initiated early (<48 hours) during hospitalization in hemodynamically stable patients who are post-MI with reduced LVEF or heart failure. • Calcium channel blockers may be considered in patients with HF who have angina despite the optimal use of β-blockers and nitrates. <u>Managing heart failure in the elderly, women and African Americans</u> • Standard regimens of ACE inhibitors and β-blockers are recommended in elderly patients with heart failure. • ACE inhibitor and β-blocker therapy are recommended in all women with heart failure and left ventricular systolic dysfunction. • ACE inhibitor and β-blocker therapy are recommended in all African American patients with heart failure and left ventricular systolic dysfunction. ARBs may be substituted in patients who are intolerant to ACE inhibitors. <u>Heart failure in patients with reduced ejection fraction</u> • ACE inhibitors are recommended in asymptomatic patients with reduced LVEF (<40%). • ARBs may be used in patients who are intolerant to ACE inhibitors. • β-blockers shown to be effective in clinical trials of patients with heart failure are recommended for patients with a LVEF ≤40%. • The combination of a β-blocker and an ACE inhibitor is recommended as routine therapy for asymptomatic patients with a LVEF ≤40%. The evidence is stronger in patients with a history of MI. • β-blocker therapy is recommended for patients with a recent decompensation of heart failure after optimization of volume status and successful discontinuation of intravenous diuretics and vasoactive drugs. Whenever possible, β-blocker therapy should be initiated in the hospital setting at a low dose prior to discharge of stable patients. • β-blocker therapy is recommended in the great majority of patients with heart failure and reduced LVEF, even if there is concurrent diabetes, chronic obstructive pulmonary disease or peripheral vascular disease. Caution may be warranted in these patients.

Clinical Guideline	Recommendation(s)
	• It is recommended that β blockade be initiated at low doses and uptitrated gradually. • It is recommended that β-blocker therapy be continued in most patients experiencing a symptomatic exacerbation of heart failure during chronic maintenance treatment, unless they develop cardiogenic shock, refractory volume overload or symptomatic bradycardia. • The routine use of an ARB is not recommended in addition to an ACE inhibitor and a β-blocker in patients with a recent acute MI and reduced LVEF. • The addition of an ARB should be considered in patients with heart failure due to reduced LVEF who have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor and a β-blocker. • Administration of an aldosterone antagonist is recommended for patients with NYHA class IV (or class III, previously class IV) HF from reduced LVEF (<35%) while receiving standard therapy, including diuretics. • Diuretic therapy is recommended to restore and maintain normal volume status in patients with clinical evidence of fluid overload, generally manifested by congestive symptoms or signs of elevated filling pressures. Loop diuretics rather than thiazide-type diuretics are typically necessary to restore normal volume status in patients with heart failure. • The initial dose of diuretic may be increased as necessary to relieve congestion, and restoration of normal volume status may require multiple adjustments, especially in patients with severe fluid overload evidenced by massive edema or ascites. After a diuretic effect is achieved with loop diuretics (short acting), increasing administration frequency to twice or even three times/day will provide more diuresis with less physiologic perturbation than larger single doses. • Oral torsemide may be considered in patients in whom poor absorption of oral medication or erratic diuretic effect may be present. Particularly in patients with right-sided heart failure and refractory fluid retention despite high doses of other loop diuretics. • Intravenous administration of diuretics may be necessary to relieve congestion. • Diuretic refractoriness may represent patient nonadherence, a direct effect of diuretic use on the kidney or progression of underlying cardiac dysfunction. • Addition of chlorothiazide or metolazone, once or twice daily, to loop diuretics should be considered in patients with persistent fluid retention despite high dose loop diuretic therapy. Chronic daily use should be avoided if possible because of the potential for electrolyte shifts and volume depletion. These drugs may be used periodically (every other day or weekly) to optimize fluid management. Metolazone will generally be more potent and much longer acting in this setting and in patients with chronic renal insufficiency, so administration should be adjusted accordingly. Volume status and electrolytes must be monitored closely when multiple diuretics are used. • Careful observation for the development of side effects is recommended in patients treated with diuretics, especially when high doses or combination therapy are used. Patients should undergo routine laboratory studies and clinical examination as dictated by their clinical response. • Patients requiring diuretic therapy to treated fluid retention associated with heart failure generally require chronic treatment, although often at lower doses than those required initially to achieve diuresis. Decreasing or discontinuing therapy may be considered in patients experiencing significant improvement in clinical status and cardiac function or in those who successfully restrict dietary sodium intake. These patients may undergo cautious weaning of diuretic dose and frequency with careful observation for recurrent fluid retention. • Patients and caregivers should be given education on the early signs of fluid retention and the plan for initial therapy. • Selected patients may be educated to adjust daily dose of diuretic in response to

Clinical Guideline	Recommendation(s)

	weight gain from fluid overload.
	
	Evaluation and management of patients with acute decompensated heart failure
	• Patients admitted with acute decompensated heart failure and evidence of fluid overload be treated initially with loop diuretics; usually given intravenously rather than orally. Ultrafiltration may be considered in lieu of diuretics.
	• Diuretics should be administered at doses needed to produce a rate of diuresis sufficient to achieve optimal volume status with relief of signs and symptoms of congestion, without inducing an excessively rapid reduction in intravascular volume or serum electrolytes.
	• Monitoring of daily weights, intake and output is recommended to assess clinical efficacy of diuretic therapy.
	• Careful observation for development of a variety of side effects, including renal dysfunction, electrolyte abnormalities, symptomatic hypotension and gout is recommended in patients treated with diuretics, especially when high doses or combination therapy is used.
	• Careful observation for the development of renal dysfunction is recommended in patients treated with diuretics. Patients with moderate to severe renal dysfunction and evidence of fluid retention should continue to be treated with diuretics. In the presence of severe fluid overload, renal dysfunction may improve with diuresis.
	• When congestion fails to improve in response to diuretic therapy, the following options should be considered:
	  ○ Re-evaluating the presence/absence of congestion.
	  ○ Sodium and fluid restriction.
	  ○ Increasing doses of loop diuretic.
	  ○ Continuous infusion of a loop diuretic.
	  ○ Addition of a second type of diuretic orally (metolazone or spironolactone) or intravenously (chlorothiazide).
	  ○ Ultrafiltration may be considered as well.

European Society of Cardiology: **Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (2016)**[9]	Pharmacological treatments indicated in patients with symptomatic (NYHA Class II-IV) heart failure with reduced ejection fraction • An ACE inhibitor is recommended, in addition to a beat-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death. • A mineralocorticoid receptor antagonist 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. • Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion. • 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. • 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

Clinical Guideline	Recommendation(s)
	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. • 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 heart failure with preserved ejection fraction and heart failure with mid-range ejection fraction</u> • It is recommended to screen patients with HFpEF or HFmrEF (mid-range) 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 or HFmrEF in order to alleviate symptoms and signs. <u>Recommendations for initial management of a rapid ventricular rate in patients with heart failure and atrial fibrillation in the acute or chronic setting</u> • Urgent electrical cardioversion is recommended if AF is thought to be contributing to the patient's hemodynamic compromise in order to improve the patient clinical condition. • For patients in NYHA Class IV, in addition to treatment for acute HF, an intravenous bolus of amiodarone or, in digoxin-naïve patients, an intravenous bolus of digoxin should be considered to reduce the ventricular rate. • For patients in NYHA Class I–III, a β-blocker, usually given orally, is safe and therefore is recommended as first-line treatment to control ventricular rate, provided the patient is euvolemic. • For patients in NYHA Class I–III, digoxin should be considered when ventricular rate remains high despite β-blockers or when β-blockers are not tolerated or contraindicated. • Treatment with dronedarone to improve ventricular rate control is not recommended due to safety concerns. <u>Recommendations for cardiac imaging in patients with suspected or established heart failure</u> • Transthoracic Echocardiogram (TTE) is recommended for the assessment of myocardial structure and function in subjects with suspected HF in order to establish a diagnosis of HFrEF, HFmrEF, or HFpEF. • TTE is recommended for the assessment of LVEF in order to identify patients with HF who would be suitable for evidence-based pharmacological and device treatment recommended for HFrEF. <u>Recommendations aiming to prevent or delay the development of overt heart failure or prevent death before the onset of symptoms</u> • Treatment of hypertension is recommended to prevent or delay the onset of HF

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	and prolong life. • ACE inhibitor is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction in order to prevent or delay the onset of HF and prolong life. • Beta-blocker is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction, in order to prevent or delay the onset of HF and prolong life. Pharmacological treatments indicated in patients with symptomatic 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 β-blocker is recommended, in addition to an ACE inhibitor, for patients with stable, symptomatic HFrEF to reduce the risk of HF hospitalization and death. • A mineralocorticoid receptor antagonist 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. Other pharmacological treatments recommended in selected patients with symptomatic heart failure with reduced ejection fraction • Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion. • 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. Treatments (or combinations of treatments) that may cause harm in patients with symptomatic (New York Heart Association Class II–IV) heart failure with reduced ejection fraction • Diltiazem or verapamil are not recommended in patients with HFrEF, as they increase the risk of HF worsening and HF hospitalization. • The addition of an ARB (or a renin inhibitor) to the combination of an ACE inhibitor and a mineralocorticoid receptor antagonist is not recommended in patients with HF, because of the increased risk of renal dysfunction and hyperkalemia. Not-recommended treatments of co-morbidities in patients with heart failure • Thiazolidinediones (glitazones) are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization. • NSAIDs or COX-2 inhibitors are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization. Recommendations for the 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. • In patients with new-onset AHF or those with chronic, decompensated HF not receiving oral diuretics the initial recommended dose should be 20 to 40 mg intravenous furosemide (or equivalent); for those on chronic diuretic therapy, initial intravenous dose should be at least equivalent to oral dose. • It is recommended to give diuretics either as intermittent boluses or a continuous infusion, and the dose and duration should be adjusted according to the patients'

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	symptoms and clinical status. • Inotropic agents are not recommended unless the patient is symptomatically hypotensive or hypoperfused because of safety concern.
Eighth Joint National Committee (JNC 8): **2014 Evidence-based Guideline for the Management of High Blood Pressure in Adults (2014)**[10]	• 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.
American Society of Hypertension/ International Society of Hypertension: **Clinical Practice Guidelines for the Management of Hypertension in the Community (2014)**[11]	Nonpharmacologic treatment • In patients with hypertension that is no more severe than stage one and is not associated with evidence of abnormal cardiovascular findings or other cardiovascular risks, six to 12 months of lifestyle changes can be attempted in the hope that they may be sufficiently effective to make it unnecessary to use medicines. • It may be prudent to start treatment with drugs sooner if it is clear that the blood pressure is not responding to the lifestyle methods or if other risk factors appear. • Weight loss: In patients who are overweight or obese, weight loss is helpful in treating hypertension, diabetes, and lipid disorders. • Salt reduction: Reduction of salt intake is recommended because it can reduce blood pressure and decrease the need for medications in patients who are "salt sensitive." • Exercise: Regular aerobic exercise can help reduce blood pressure.

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	• Alcohol consumption: Up to two drinks a day can be helpful in protecting against cardiovascular events, but greater amounts of alcohol can raise blood pressure and should therefore be discouraged. In women, alcohol should be limited to one drink a day.
	• Cigarette smoking: Stopping smoking will not reduce blood pressure, but since smoking by itself is such a major cardiovascular risk factor, patients must be strongly urged to discontinue this habit.
	
	<u>Drug treatment of hypertension</u>
	• Treatment with drugs should be started in patients with blood pressures >140/90 mm Hg in whom lifestyle treatments have not been effective.
	• In patients with stage two hypertension (blood pressure ≥160/100 mm Hg), drug treatment should be started immediately after diagnosis, usually with a two-drug combination, without waiting to see the effects of lifestyle changes.
	• For patients older than 80 years, the suggested threshold for starting treatment is at levels ≥150/90 mm Hg. Thus, the target of treatment should be <140/90 mm Hg for most patients but <150/90 mm Hg for older patients (unless these patients have chronic kidney disease or diabetes, when <140/90 mm Hg can be considered).
	• Most patients will require more than one drug to achieve control of their blood pressure.
	• In general, increase the dose of drugs or add new drugs at approximately two to three week intervals. This frequency can be faster or slower depending on the judgment of the practitioner. In general, the initial doses of drugs chosen should be at least half of the maximum dose so that only one dose adjustment is required thereafter. It is generally anticipated that most patients should reach an effective treatment regimen, whether one, two, or three drugs, within six to eight weeks.
	• Choice of drugs should be influenced by the age, ethnicity/race, and other clinical characteristics of the patient.
	• The choice of drugs will also be influenced by other conditions (e.g., diabetes and coronary disease) associated with the hypertension. Pregnancy also influences drug choice.
	• Long-acting drugs that need to be taken only once daily are preferred to shorter-acting drugs that require multiple doses because patients are more likely to follow a simple treatment regimen.
	• This guideline only makes recommendations for drug classes, not individual agents. There is an assumption, unless otherwise stated, that all drugs in a class are similar to each other.
	• Drug selectin when hypertension is the only or main concern:
	  ○ For black patients of all ages, use calcium channel blocker (CCB) or thiazide diuretic as first drug, then add angiotensin receptor blocker (ARB) or angiotensin-converting enzyme (ACE) inhibitor if needed.
	  ○ For white and other non-black patients <60 years of age, use ARB or ACE inhibitor as first drug, then add CCB or thiazide diuretic if needed.
	  ○ For white and other non-black patients ≥60 years of age, use CCB or thiazide diuretic as first drug, then add ARB or ACE inhibitor if needed.
	• Drug selection when hypertension is associated with other conditions:
	  ○ For patients with hypertension and diabetes, use ARB or ACE inhibitor as first drug (note, in black patients it is acceptable to start with a CCB or thiazide), then add CCB or thiazide diuretic (unless starting on CCB or thiazide in black patients) if needed.
	  ○ For patients with hypertension and chronic kidney disease, use ARB or ACE inhibitor as first drug, then add CCB or thiazide diuretic if needed.
	  ○ For patients with hypertension and clinical coronary artery disease, use β-blocker plus ARB or ACE inhibitor as first drugs, then add CCB or thiazide diuretic if needed.

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	○ For patients with hypertension and stroke history, use ACE inhibitor or ARB as first drug, then add thiazide diuretic or CCB if needed. • For patients with hypertension and heart failure, patients with h symptomatic heart failure should usually receive an ARB or ACE inhibitor plus β-blocker plus diuretic plus spironolactone regardless of blood pressure. A dihydropyridine CCB can be added if needed for blood pressure control.
Hypertension Canada: **2017 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults (2017)**[12]	<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. <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>Guidelines for individuals 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

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	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. • 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

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	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.
	
	Treatment of hypertension in association with stroke
	• BP management in acute ischemic stroke (onset to 72 hours)
	  ○ For patients with ischemic stroke not eligible for thrombolytic therapy, treatment of hypertension in the setting of acute ischemic stroke or transient ischemic attack should not be routinely undertaken. Extreme BP increases (e.g., SBP >220 mmHg or DBP >120 mmHg) may be treated to reduce the BP by approximately 15%, and not more than 25%, over the first 24 hours with gradual reduction thereafter. Avoid excessive lowering of BP because this might exacerbate existing ischemia or might induce ischemia, particularly in the setting of intracranial arterial occlusion or extracranial carotid or vertebral artery occlusion. Pharmacological agents and routes of administration should be chosen to avoid precipitous decreases in BP.
	  ○ For patients with ischemic stroke eligible for thrombolytic therapy, very high BP (>185/110 mmHg) should be treated concurrently in patients receiving thrombolytic therapy for acute ischemic stroke to reduce the risk of secondary intracranial hemorrhage.
	• 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)
	  ○ For patients with intracerebral hemorrhage (ICH) in the hyperacute phase (in the first 24 hours) SBP lowering to <140 mmHg should be avoided because of an absence of benefit (relative to a target of <180 mmHg) and some suggestion of harm.
	
	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
	• For patients with nondiabetic chronic kidney disease, target BP is <140/90 mmHg.
	• For patients with hypertension and proteinuric chronic kidney disease (urinary protein >500 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.
	• Thiazide/thiazide-like diuretics are recommended as additive antihypertensive therapy. For patients with chronic kidney disease and volume overload, loop diuretics are an alternative.
	• 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.

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	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. • In patients with hypertension attributable to FMD-related renal artery stenosis, revascularization should be considered. • 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 2 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. Combination therapy using two first-line agents may also be considered as initial treatment of hypertension if SBP is 20 mmHg greater than target or if DBP is 10 mmHg greater than target. However, caution should be exercised in patients in whom a substantial decrease in BP is more likely or poorly tolerated (e.g., elderly patients and patients with autonomic neuropathy). • 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.
European Society of Hypertension/European Society of Cardiology: **2013 Guidelines for the management of arterial hypertension (2013)[13]**	The 2013 guidelines on hypertension of the European Society of Hypertension and the European Society of Cardiology follow the guidelines jointly issued by the two societies in 2003 and 2007. Treatment strategies and choice of antihypertensive drugs • Diuretics (including thiazides, chlorthalidone, and indapamide), β-blockers, calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) are all suitable for the initiation and maintenance of antihypertensive treatment, either as monotherapy or in some combinations. • Some agents should be considered as the preferential choice in specific conditions because used in trials in those conditions or because of greater effectiveness in specific types of organ damage. • Initiation of antihypertensive therapy with a two-drug combination may be considered in patients with markedly high baseline blood pressure (BP) or at high cardiovascular (CV) risk. • The combination of two antagonists of the renin-angiotensin system (RAS) is not recommended and should be discouraged. • Other drug combinations should be considered and probably are beneficial in

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	proportion to the extent of BP reduction. However, combinations that have been successfully used in trials may be preferable. • Combinations of two antihypertensive drugs at fixed doses in a single tablet may be recommended and favored, because reducing the number of daily pills improves adherence, which is low in patients with hypertension. <u>Treatment strategies in white-coat and masked hypertension</u> • In white-coat hypertensives without additional risk factors, therapeutic intervention may be limited to lifestyle changes only, but this decision should be accompanied by close follow-up. • In white-coat hypertensives with a higher CV risk because of metabolic derangements or asymptomatic organ damage, drug treatment may be considered in addition to lifestyle changes. • In masked hypertension, both lifestyle measures and antihypertensive drug treatment should be considered, because this type of hypertension has been consistently found to have a CV risk very close to that of in- and out-of-office hypertension. <u>Antihypertensive treatment strategies in the elderly</u> • In elderly hypertensives with SBP ≥160 mmHg there is solid evidence to recommend reducing SBP to between 150 and 140 mmHg. • In fit elderly patients <80 years old antihypertensive treatment may be considered at SBP values ≥140 mmHg with a target SBP <140 mmHg if treatment is well tolerated. • In individuals older than 80 years with an initial SBP ≥160 mmHg, it is recommended to reduce SBP to between 150 and 140 mmHg, provided they are in good physical and mental conditions. • In frail elderly patients, it is recommended to leave decisions on antihypertensive therapy to the treating physician, and based on monitoring of the clinical effects of treatment. • Continuation of well-tolerated antihypertensive treatment should be considered when a treated individual becomes an octogenarian. • All hypertensive agents are recommended and can be used in the elderly, although diuretics and calcium antagonists may be preferred in isolated systolic hypertension. <u>Treatment strategies in hypertensive women</u> • Hormone therapy and selective estrogen receptor modulators are not recommended and should not be used for primary or secondary prevention of CVD. • If treatment of younger perimenopausal women is considered for severe menopausal symptoms, the benefits should be weighed against potential risks. • Drug treatment of severe hypertension in pregnancy (SBP >160 mmHg or DBP >110 mmHg) is recommended. • Drug treatment may also be considered in pregnant women with persistent elevation of BP ≥150/95 mmHg, and in those with BP ≥140/90 mmHg in the presence of gestational hypertension, subclinical organ damage or symptoms. • In women at high risk of pre-eclampsia, provided they are at low risk of gastrointestinal hemorrhage, treatment with low dose aspirin from 12 weeks until delivery may be considered. • In women with child-bearing potential RAS blockers are not recommended and should be avoided. • Methyldopa, labetalol, and nifedipine should be considered preferential antihypertensive drugs in pregnancy. Intravenous labetalol or infusion of nitroprusside should be considered in case of emergency (pre-eclampsia).

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	<u>Treatment strategies in patients with diabetes</u> • While initiation of antihypertensive drug treatment in diabetic patients whose SBP is ≥160 mmHg is mandatory, it is strongly recommended to start drug treatment also when SBP is ≥140 mmHg. • A SBP goal <140 mmHg is recommended in patients with diabetes. • The DBP target in patients with diabetes is recommended to be <85 mmHg. • All classes of antihypertensive agents are recommended and can be used in patients with diabetes; RAS blockers may be preferred, especially in the presence of proteinuria or microalbuminuria. • It is recommended that individual drug choice takes comorbidities into account. • Simultaneous administration of two blockers of the RAS is not recommended and should be avoided in patients with diabetes <u>Treatment strategies in hypertensive patients with metabolic syndrome</u> • Lifestyle changes, particularly weight loss and physical exercise, are to be recommended to all individuals with the metabolic syndrome. These interventions improve not only BP, but the metabolic components of the syndrome and delay diabetes onset. • As the metabolic syndrome can be considered a 'pre-diabetic' state, antihypertensive agents potentially improving or at least not worsening insulin sensitivity, such as RAS blockers and calcium antagonists, should be considered as the preferred drugs. Beta-blockers (with the exception of vasodilating β-blockers) and diuretics should be considered only as additional drugs, preferably in association with a potassium-sparing agent. • It is recommended to prescribe antihypertensive drugs with particular care in hypertensive patients with metabolic disturbances when BP is ≥140/90 mmHg after a suitable period of lifestyle changes, and to maintain BP <140/90 mmHg. • BP lowering drugs are not recommended in individuals with metabolic syndrome and high normal BP. <u>Therapeutic strategies in hypertensive patients with nephropathy</u> • Lowering SBP to <140 mmHg should be considered. • When overt proteinuria is present, SBP values <130 mmHg may be considered, provided that changes in eGFR are monitored. • RAS blockers are more effective in reducing albuminuria than other antihypertensive agents, and are indicated in hypertensive patients in the presence of microalbuminuria or overt proteinuria. • Reaching BP goals usually requires combination therapy, and it is recommended to combine RAS blockers with other antihypertensive agents. • Combination of two RAS blockers, though potentially more effective in reducing proteinuria, is not recommended. • Aldosterone antagonists cannot be recommended in chronic kidney disease (CKD), especially in combination with a RAS blocker, because of the risk of excessive reduction in renal function and of hyperkalemia. <u>Therapeutic strategies in hypertensive patients with cerebrovascular disease</u> • It is not recommended to intervene with BP-lowering therapy during the first week after acute stroke irrespective of BP level, although clinical judgement should be used in the face of very high SBP values. • Antihypertensive treatment is recommended in hypertensive patients with a history of stroke or transient ischemic attack (TIA), even when initial SBP is in the 140 to 159 mmHg range. • In hypertensive patients with a history of stroke or TIA, a SBP goal of <140 mmHg should be considered.

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	• In elderly hypertensives with previous stroke or TIA, SBP values for intervention and goal may be considered to be somewhat higher. • All drug regimens are recommended for stroke prevention, provided that BP is effectively reduced. <u>Therapeutic strategies in hypertensive patients with heart disease</u> • In hypertensive patients with CHD, a SBP goal <140 mmHg should be considered. • In hypertensive patients with a recent myocardial infarction, β-blockers are recommended. In case of other CHD all antihypertensive agents can be used, but β-blockers and calcium antagonists are to be preferred for symptomatic reasons (angina). • Diuretics, β-blockers, ACE inhibitors, angiotensin receptor blockers, and/or mineralocorticoid receptor antagonists are recommended in patients with heart failure or severe left ventricular (LV) dysfunction to reduce mortality and hospitalization. • In patients with heart failure and preserved ejection fraction (EF), there is no evidence that antihypertensive therapy per se or any particular drug is beneficial. However, in these patients, as well as in patients with hypertension and systolic dysfunction, lowering SBP to around 140 mmHg should be considered. Treatment guided by relief of symptoms (congestion with diuretics, high heart rate with β-blockers, etc.) should also be considered. • ACE inhibitors and angiotensin receptor blockers (and β-blockers and mineralocorticoid receptor antagonists if heart failure coexists) should be considered as antihypertensive agents in patients at risk of new or recurrent atrial fibrillation. • It is recommended that all patients with left ventricular hypertrophy (LVH) receive antihypertensive agents. • In patients with LVH, initiation of treatment with one of the agents that have shown a greater ability to regress LVH should be considered, i.e. ACE inhibitors, angiotensin receptor blockers, and calcium antagonists. <u>Therapeutic strategies in hypertensive patients with atherosclerosis, arteriosclerosis, and peripheral artery disease (PAD)</u> • In the presence of carotid atherosclerosis, prescription of calcium antagonists and ACE inhibitors should be considered as these agents have shown a greater efficacy in delaying atherosclerosis progression than diuretics and β-blockers. • In hypertensive patients with a pulse wave velocity above 10 m/s, all antihypertensive drugs should be considered provided that a BP reduction to <140/90 mmHg is consistently achieved. • Antihypertensive therapy is recommended in hypertensive patients with PAD to achieve a goal of <140/90 mmHg, because of their high risk of myocardial infarction, stroke, heart failure, and CV death. • Though a careful follow up is necessary, β-blockers may be considered for the treatment of arterial hypertension in patients with PAD, since their use does not appear to be associated with exacerbation of PAD symptoms.
National Institute for Health and Clinical Excellence: **Hypertension in adults: diagnosis and management (2011)**[14] **Reaffirmed Nov 2016**	<u>Choosing antihypertensive drug treatment</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 people ≥80 years of age the same antihypertensive drug treatment as people aged 55 to 80 years, taking into account any comorbidities. • Offer antihypertensive drug treatment to women of child-bearing potential in line with the recommendations on Management of pregnancy with chronic

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	hypertension and Breastfeeding in 'Hypertension in pregnancy' (NICE clinical guideline 107).
	
	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). 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 step one antihypertensive (ACE inhibitor, ARB) with a calcium channel blocker (CCB) to patients >55 years of age and to black patients of African or Caribbean family origin 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 chlorthalidone (12.5 to 25.0 mg once daily) or indapamide (1.5 mg modified-release once daily or 2.5 mg once daily) in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide.
	• For patients who are already receiving treatment with bendroflumethiazide or hydrochlorothiazide and whose blood pressure is stable and well controlled, continue treatment as is.
	• β-blockers are not a preferred initial therapy for hypertension; however, β-blockers may be considered in younger patients, particularly:
	  ○ Patients with an intolerance or contraindication to ACE inhibitors and ARBs.
	  ○ Women of child-bearing potential.
	  ○ People with evidence of increased sympathetic drive.
	• If treatment is initiated with a β-blocker and a second antihypertensive is required, add a CCB over a thiazide-like diuretic to reduce the risk of developing diabetes.
	
	Step two treatment
	• If blood pressure is not controlled with a step one antihypertensive, offer a step two treatment with a CCB in combination with an ACE inhibitor or an ARB.
	• If a CCB is not appropriate or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic.
	• For black patients of African or Caribbean family origin, consider an ARB in preference to an ACE inhibitor, in combination with a CCB.
	
	Step three treatment
	• Before considering step three treatment, review medication to ensure step two treatment is at optimal or best tolerated doses.
	• If three drugs are required to control blood pressure, the combination of an ACE inhibitor or ARB, CCB, and thiazide-like diuretic should be utilized.
	
	Step four treatment
	• Regard clinic blood pressure that remains >140/90 mmHg after treatment with the optimal or best tolerated doses of an ACE inhibitor or an ARB plus a CCB plus a diuretic as resistant hypertension, and consider adding a fourth antihypertensive drug and/or seeking expert advice.
	• For treatment of resistant hypertension at step four:
	  ○ Consider further diuretic therapy with low-dose spironolactone (25 mg once daily) if the blood potassium level is 4.5 mmol/l or lower. Use particular caution in people with a reduced estimated glomerular filtration rate because they have an increased risk of hyperkalemia.
	  ○ Consider higher-dose thiazide-like diuretic treatment if the blood potassium level is higher than 4.5 mmol/l.

Clinical Guideline	Recommendation(s)
	○ If further diuretic therapy for resistant hypertension is not tolerated or is contraindicated or ineffective, consider an α-blocker or β-blocker.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in Blacks (2010)**[15]	• 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 (2012)**[16]	<u>Blood pressure management in chronic kidney disease (CKD) non-dialysis (ND) patients without diabetes mellitus</u> • The Work Group recommends that non-diabetic adults with CKD ND and urine albumin excretion <30 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >140 mm Hg systolic or >90 mm Hg diastolic be treated with blood pressure -lowering drugs to maintain a blood pressure that is consistently ≤140 mm Hg systolic and ≤90 mm Hg diastolic. • The Work Group suggests that non-diabetic adults with CKD ND and urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with BP-lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic. • The Work Group suggests that non-diabetic adults with CKD ND and urine albumin excretion >300 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with blood pressure -lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤ 80 mm Hg diastolic. • The Work Group suggests that an angiotensin receptor blocker (ARB) or angiotensin converting enzyme inhibitor (ACE-I) be used in non-diabetic adults with CKD ND and urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*) in whom treatment with blood pressure -lowering drugs is indicated. • The Work Group recommends that an ARB or ACE-I be used in non-diabetic adults with CKD ND and urine albumin excretion >300 mg per 24 hours (or equivalent*) in whom treatment with blood pressure -lowering drugs is indicated. <u>Blood pressure management in CKD ND patients with diabetes mellitus</u> • The Work Group recommends that adults with diabetes and CKD ND with urine albumin excretion <30 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >140 mm Hg systolic or >90 mm Hg diastolic be treated with BP-lowering drugs to maintain a blood pressure that is consistently ≤140 mm

Clinical Guideline	Recommendation(s)
	Hg systolic and ≤90 mm Hg diastolic. • The Work Group suggests that adults with diabetes and CKD ND with urine albumin excretion >30 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with BP-lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic. • The Work Group suggests that an ARB or ACE-I be used in adults with diabetes and CKD ND with urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*). • The Work Group recommends that an ARB or ACE-I be used in adults with diabetes and CKD ND with urine albumin excretion >300 mg per 24 hours (or equivalent*). <u>Blood pressure management in kidney transplant recipients (non–dialysis-dependent CKD of any stage with a kidney transplant [CKD T])</u> • The Work Group suggests that adult kidney transplant recipients whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic, irrespective of the level of urine albumin excretion. • In adult kidney transplant recipients, choose a blood pressure -lowering agent after taking into account the time after transplantation, use of calcineurin inhibitors, presence or absence of persistent albuminuria, and other co morbid conditions. <u>Blood pressure management in children with CKD ND</u> • The Work Group recommends that in children with CKD ND, blood pressure -lowering treatment is started when blood pressure is consistently above the 90th percentile for age, sex, and height. • The Work Group suggests that in children with CKD ND (particularly those with proteinuria), blood pressure is lowered to consistently achieve systolic and diastolic readings less than or equal to the 50th percentile for age, sex, and height, unless achieving these targets is limited by signs or symptoms of hypotension. • The Work Group suggests that an ARB or ACE-I be used in children with CKD ND in whom treatment with blood pressure -lowering drugs is indicated, irrespective of the level of proteinuria. <u>Blood pressure management in elderly persons with CKD ND</u> • Tailor blood pressure treatment regimens in elderly patients with CKD ND by carefully considering age, co-morbidities and other therapies, with gradual escalation of treatment and close attention to adverse events related to blood pressure treatment, including electrolyte disorders, acute deterioration in kidney function, orthostatic hypotension and drug side effects. *Approximate equivalents for albumin excretion rate per 24 hours is expressed as protein excretion rate per 24 hours, albumin/creatinine ratio, protein/creatinine ratio, and protein reagent strip results.
American Diabetes Association: **Standards of Medical Care in Diabetes (2017)**[17]	<u>Hypertension/blood pressure control</u> • Blood pressure should be measured at every routine visit. Patients found to have elevated blood pressure should have blood pressure confirmed on a separate day. • Most patients with diabetes and hypertension should be treated to a systolic blood pressure goal of <140 mmHg and a diastolic blood pressure goal of <90 mmHg. • Lower systolic and diastolic blood pressure targets, such as 130/80 mmHg, may be appropriate for individuals at high risk of cardiovascular disease, if they can be achieved without undue treatment burden. • In pregnant patients with diabetes and chronic hypertension, blood pressure targets of 120 to 160/80 to 105 mmHg are suggested in the interest of optimizing long-

Clinical Guideline	Recommendation(s)
	term maternal health and minimizing impaired fetal growth. • Patients with confirmed office-based blood pressure >140/90 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). 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. • For patients with blood pressure >120/80 mmHg, lifestyle intervention consists of weight loss if overweight or obese; a Dietary Approaches to Stop Hypertension–style dietary pattern including reducing sodium and increasing potassium intake; moderation of alcohol intake; and increased physical activity. <u>Coronary heart disease</u> • In asymptomatic patients, routine screening for coronary artery disease is not recommended as it does not improve outcomes as long as atherosclerotic cardiovascular disease risk factors are treated. • Consider investigations for coronary artery disease in the presence of any of the following: atypical cardiac symptoms (e.g., unexplained dyspnea, chest discomfort); signs or symptoms of associated vascular disease including carotid bruits, transient ischemic attack, stroke, claudication, or peripheral arterial disease; or electrocardiogram abnormalities (e.g., Q waves). • In patients with known atherosclerotic cardiovascular disease, use aspirin and statin therapy (if not contraindicated) and consider ACE inhibitor therapy to reduce the risk of cardiovascular events. • In patients with prior myocardial infarction, β-blockers should be continued for at least two years after the event. • In patients with symptomatic heart failure, thiazolidinedione treatment should not be used. • In patients with type 2 diabetes with stable congestive heart failure, metformin may be used if estimated glomerular filtration remains >30 mL/min but should be avoided in unstable or hospitalized patients with congestive heart failure. <u>Diabetic 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, in all patients with type 2 diabetes, and in all patients with comorbid hypertension. • Optimize glucose control to reduce the risk or slow the progression of diabetic kidney disease. • Optimize blood pressure control to reduce the risk or slow the progression of

Clinical Guideline	Recommendation(s)
	diabetic kidney disease. • For people with nondialysis-dependent diabetic kidney disease, dietary protein intake should be approximately 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. • 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) B 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 or changes in potassium when ACE inhibitors, angiotensin receptor blockers, or diuretics are used. • Continued monitoring of urinary albumin–to–creatinine ratio in patients with albuminuria treated with an ACE inhibitor or an angiotensin receptor blocker is reasonable to assess the response to treatment and progression of diabetic kidney disease. • An ACE inhibitor or an angiotensin receptor blocker is not recommended for the primary prevention of diabetic kidney disease 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. • When estimated glomerular filtration rate is <60 mL/min/1.73 m^2, evaluate and manage potential complications of chronic kidney disease. • Patients should be referred for evaluation for renal replacement treatment if they have an estimated glomerular filtration rate <30 mL/min/1.73 m^2. • Promptly refer to a physician experienced in the care of kidney disease for uncertainty about the etiology of kidney disease, difficult management issues, and rapidly progressing kidney disease.
American Association for the Study of Liver Diseases: **Management of Adult Patients with Ascites Due to Cirrhosis: Update 2012 (2012)[18]** **[Reaffirmed Oct 2014]**	Treatment of ascites • First line treatment of patients with cirrhosis and ascites consists of sodium restriction (88 mmol/day [2,000 mg/day]) and diuretics (oral spironolactone with or without oral furosemide). • Fluid restriction is not necessary unless serum sodium is <125 mmol/L. • Vasopressin antagonists may improve serum sodium in patients with cirrhosis and ascites. However their use does not currently appear justified in view of their expense, potential risks, and lack of evidence of efficacy in clinically meaningful outcomes. • An initial therapeutic abdominal paracentesis should be performed in patients with tense ascites. Sodium restriction and oral diuretics should then be initiated. • Diuretic-sensitive patients should preferably be treated with sodium restriction and oral diuretics rather than with serial paracentesis. • Use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers in patients with cirrhosis and ascites may be harmful and must be carefully considered in each patient, monitoring blood pressure and renal function. • The use of nonsteroidal anti-inflammatory drugs should be avoided in patients with cirrhosis and ascites, except in special circumstances. • Liver transplantation should be considered in patients with cirrhosis and ascites.

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	Chloro-thiazide*	HCTZ*	Methyclo-thiazide*
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[5]

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
Methyclothiazide	Rapid	Not reported	Not reported	Renal	Not reported

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[5]

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, methyclothiazide)	Digitalis glycosides	Thiazide diuretics may induce electrolyte disturbances which may predispose patients to digitalis-induced arrhythmias.
Thiazide diuretics (chlorothiazide, HCTZ, methyclothiazide)	Dofetilide	Thiazide diuretics may induce hypokalemia which may increase the risk of torsades de pointes.
Thiazide diuretics (chlorothiazide, HCTZ, methyclothiazide)	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, methyclothiazide)	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.

Generic Name(s)	Interaction	Mechanism
methyclothiazide)		
Thiazide diuretics (chlorothiazide, methyclothiazide)	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[1-5]

Adverse Events	Chlorothiazide	HCTZ	Methyclothiazide
Cardiovascular			
Hypotension	✔	✔	-
Necrotizing angiitis	✔	✔	✔
Orthostatic hypotension	✔	✔	✔
Central Nervous System			
Dizziness	✔	✔	✔
Fever	✔	✔	✔
Headache	✔	✔	✔
Restlessness	✔	✔	✔
Vertigo	✔	✔	✔
Dermatological			
Alopecia	✔	✔	-
Cutaneous vasculitis	-	✔	✔
Erythema multiforme	✔	✔	<1
Exfoliative dermatitis	✔	✔	-
Photosensitivity	✔	✔	✔
Purpura	✔	✔	✔
Rash	✔	✔	✔
Stevens-Johnson syndrome	✔	✔	✔
Toxic epidermal necrolysis	✔	✔	-
Urticaria	✔	✔	✔
Vasculitis	-	✔	✔
Gastrointestinal			
Abdominal cramping	✔	✔	✔
Anorexia	✔	✔	✔
Constipation	✔	✔	✔
Diarrhea	✔	✔	✔
Epigastric distress	-		-
Gastric irritation	✔	✔	✔
Nausea	✔	✔	✔
Pancreatitis	✔	✔	✔
Sialadenitis	✔	✔	✔
Vomiting	✔	✔	✔
Genitourinary			
Impotence	✔	✔	-

Adverse Events	Chlorothiazide	HCTZ	Methyclothiazide
Hematologic			
Agranulocytosis	✔	✔	✔
Aplastic anemia	✔	✔	✔
Hemolytic anemia	✔	✔	✔
Leukopenia	✔	✔	✔
Thrombocytopenia	✔	✔	✔
Hepatic			
Hepatic function impairment	-	-	-
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			
Allergic myocarditis	-	-	-
Allergic reactions	-	-	-
Anaphylactic reactions	✔	✔	✔
Eosinophilic pneumonitis	-	-	-
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, tablet: 0.5 to 1 g once or	Safety and efficacy in children have not been	Injection: 500 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	twice daily, often administered on alternate days or on three to five days each week Hypertension: Injection, suspension, tablet: 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	established.	Suspension 250 mg/5 mL Tablet: 250 mg 500 mg
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)	Safety and efficacy in children have not been established.	Capsule: 12.5 mg Tablet: 12.5 mg 25 mg 50 mg
Methyclothiazide	Edema: Tablet: maintenance, 2.5 to 10 mg once daily; maximum, 10 mg/day Hypertension: Tablet: 2.5 to 5 mg once daily	Safety and efficacy in children have not been established.	Tablet: 5 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.[19] (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.[20] (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[21] (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.[22] (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.[23] (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.[24] (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.[25] (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

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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.[26] (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.[27] (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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(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.[28] (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.[29] (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.[30] (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[31] (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.[32] (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.[33] (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[34] (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.[35] (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; [$_3$H]-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; [$_3$H]-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.[36] (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.[37] (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.[38] (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.[39] (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.[40]	DB, MC, PC, RCT	N=512	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(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.[41] (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.[42] (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.[43] (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.[44] (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.[45] (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.[46] (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.[47] (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.[48] (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.[49] (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.[50] (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.[51] (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.[52] (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.[53] (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.[54] (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.[55] (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.[56] (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.[57] (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.[58] (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.[59] (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.[60] (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.[61] (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.[62] (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.[63] (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.[64] (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

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				(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.[65] (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.[66] (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.[67] (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.[68] (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.[69] (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.[70] (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.[71] (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.[72] (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.[73](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.[74] (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.[75] (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
Baguet et al.[76] (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.	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
Although cicletanine*, furosemide and spironolactone were considered for inclusion, none of the trials relating to these agents satisfied all inclusion criteria.				Secondary: Not reported
Lindholm et al.[77] (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,	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
metoprolol, oxprenolol*, pindolol, or propranolol)				
Hilleman et al.[78] (1999) Monotherapy (atenolol, HCTZ, captopril, enalapril, lisinopril, amlodipine, diltiazem, nifedipine, verapamil) vs amlodipine-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.
Wiysonge et al.[79] (2007) 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs β-blockers (atenolol, metoprolol, oxprenolol*, or propranolol)				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, 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, tablet*	Diuril®	$$	$$
HCTZ	capsule, tablet	Microzide®*	$	$
Methyclothiazide	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 is an alternative treatment option in patients experiencing gynecomastia with spironolactone. Triamterene, metolazone, and hydrochlorothiazide have also been used to treat ascites.[18]

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 published guidelines on the treatment of hypertension. Thiazide-type diuretics are frequently recommended as initial therapy in patients with uncomplicated hypertension.[10-16] 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).[10] Several guidelines consistently recommend that the selection of an antihypertensive agent be based on compelling indications for use.[10-17] Most patients will require more than one antihypertensive medication to achieve blood pressure goals.[10-16]

In clinical trials, the thiazide diuretics have been shown to effectively lower blood pressure.[23-79] 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
November 8, 2017

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 August 2015.

Table 1. Thiazide-Like Diuretics Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Chlorthalidone	tablet	N/A	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 College of Cardiology/American Heart Association: **Guideline for the Management of Heart Failure (2013)**[5]	<u>Treatment of Stage A heart failure (HF)</u> • Hypertension and lipid disorders should be controlled in accordance with guidelines to lower the risk of HF. (Level of Evidence (LoE): A) • Other conditions that may lead to or contribute to HF, such as obesity, diabetes mellitus, tobacco use, and known cardiotoxic agents, should be controlled or avoided. (LoE: C) <u>Treatment of Stage B heart failure</u> • In patients with a history of MI and reduced EF, ACE inhibitors or ARBs should be used to prevent HF. (LoE: A) • In patients with MI and reduced EF, evidence-based β-blockers (using one of three proven to reduce mortality [i.e., bisoprolol, carvedilol, and sustained-release metoprolol succinate]) should be used to prevent HF. (LoE: B) • In patients with MI, statins should be used to prevent HF. (LoE: A) • ACE inhibitors and β-blockers should be used in all patients with a reduced EF to prevent symptomatic HF, even if they do not have a history of MI. (LoE: A and C, respectively) • Blood pressure should be controlled to prevent symptomatic HF. (LoE: A) • Nondihydropyridine calcium channel blockers may be harmful in patients with

Clinical Guideline	Recommendation(s)
	low LVEF. (LoE: C) <u>Pharmacological treatment for Stage C HFrEF</u> • Recommendations for patients in Stages A and B are recommended where appropriate for patients in Stage C. (LoE: A, B, and C as appropriate) • Diuretics are recommended in patients with HFrEF who have evidence of fluid retention, unless contraindicated, to improve symptoms. (LoE: C) • ACE inhibitors are recommended in patients with HFrEF and current or prior symptoms, unless contraindicated, to reduce morbidity and mortality. ARBs are recommended as alternative therapy in ACE inhibitor intolerant patients. (LoE: A) • Use of one of the three β-blockers proven to reduce mortality is recommended for all patients with current or prior symptoms of HFrEF, unless contraindicated, to reduce morbidity and mortality. (LoE: A) • Aldosterone receptor antagonists are recommended in patients with NYHA class II–IV HF and who have LVEF of ≤35%, unless contraindicated, to reduce morbidity and mortality. Patients with NYHA class II HF should have a history of prior cardiovascular hospitalization or elevated plasma natriuretic peptide levels to be considered for aldosterone receptor antagonists. Creatinine should be ≤2.5 mg/dL in men or ≤2.0 mg/dL in women (or estimated glomerular filtration rate >30 mL/min/1.73 m^2), and potassium should be <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) • The combination of hydralazine and isosorbide dinitrate is recommended to reduce morbidity and mortality for patients self-described as African Americans with NYHA class III–IV HFrEF receiving optimal therapy with ACE inhibitors and β-blockers, unless contraindicated. (LoE: A) • Digoxin can be beneficial in patients with HFrEF, unless contraindicated, to decrease hospitalizations for HF. (LoE: B) • Patients with chronic HF with permanent/persistent/paroxysmal AF and an additional risk factor for cardioembolic stroke (history of hypertension, diabetes mellitus, previous stroke or transient ischemic attack, or ≥75 years of age) should receive chronic anticoagulant therapy. (LoE: A) • Statins are not beneficial as adjunctive therapy when prescribed solely for the diagnosis of HF in the absence of other indications for their use. (LoE: A) • Calcium channel blockers are not recommended as routine treatment for patients with HFrEF. (LoE: A) <u>Pharmacological treatment for Stage C HFpEF</u> • Blood pressure should be controlled according to published clinical practice guidelines. (LoE: B) • Diuretics should be used for relief of symptoms due to volume overload. (LoE: C) • The use of β-blocking agents, ACE inhibitors, and ARBs in patients with hypertension is reasonable to control blood pressure in patients with HFpEF. (LoE: C) <u>Treatment of Stage D (advanced/refractory) HF</u> • Fluid restriction (1.5 to 2 L/d) is reasonable, especially in patients with hyponatremia, to reduce congestive symptoms. (LoE: C) • Until definitive therapy (e.g., coronary revascularization, mechanical circulatory support, heart transplantation) or resolution of the acute precipitating problem, patients with cardiogenic shock should receive temporary intravenous inotropic support to maintain systemic perfusion and preserve end-organ performance. (LoE: C) • Continuous intravenous inotropic support is reasonable as “bridge therapy” in

Clinical Guideline	Recommendation(s)
	patients with stage D HF refractory to medical therapy and device therapy who are eligible for and awaiting mechanical circulatory support or cardiac transplantation. (LoE: B) • Long-term use of either continuous or intermittent, intravenous parenteral positive inotropic agents, in the absence of specific indications or for reasons other than palliative care, is potentially harmful in the patient with HF. (LoE: B)
Heart Failure Society of America: **Heart Failure Society of America 2010 Comprehensive Heart Failure Practice Guidelines (Executive Summary) (2010)[6]**	<u>Patients with left ventricular systolic dysfunction</u> • ACE inhibitors should be used in all patients with a LVEF ≤40%, unless otherwise contraindicated. • ARBs may be used in patients who are intolerant to ACE inhibitors. Hydralazine and a nitrate may be used in patients intolerant to ACE inhibitors and ARBs, or in whom such therapy is contraindicated. • The combination of an ACE inhibitor and a β-blocker is recommended in all patients with a LVEF ≤40%. • The routine use of an ARB with a combination of an ACE inhibitor and β-blocker in patients who have had a MI and have left ventricular dysfunction is not recommended. • The addition of an ARB can be considered in patients with heart failure due to reduced LVEF who have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor and a β-blocker. • Individual ARBs may be considered as initial therapy (instead of an ACE inhibitor) in patients with heart failure who have had a MI and in patients with chronic heart failure and systolic dysfunction. • ARBs are recommended in patients who cannot tolerate ACE inhibitors due to cough. The combination of hydralazine and an oral nitrate may be considered in such patients not tolerating ARB therapy. • Patients intolerant to ACE inhibitors from hyperkalemia or renal insufficiency are likely to experience the same side effects with ARBs. In these cases, the combination of hydralazine and an oral nitrate should be considered. • ARBs should be considered in patients experiencing angioedema while on ACE inhibitors based on their underlying risk and with recognition that angioedema has been reported infrequently with ARBs. The combination of hydralazine and oral nitrates may be considered in such patients not tolerating ARB therapy. • A combination of hydralazine and an oral nitrate is recommended in African American patients with heart failure and reduced left ventricular ejection fraction (LVEF) who are on a standard regimen of an ACE inhibitor (or ARB) and a β-blocker. • A combination of hydralazine and an oral nitrate may be considered in non–African American patients with heart failure and reduced LVEF who are symptomatic despite optimization of standard therapy. • Administration of an aldosterone antagonist is recommended for patients with New York Heart Association (NYHA) class IV (or class III, previously class IV) heart failure from reduced LVEF (<35%) while receiving standard therapy, including diuretics. • Administration of an aldosterone antagonist should be considered in patients following an acute MI, with clinical heart failure signs and symptoms or history of diabetes mellitus, and an LVEF <40%. Patients should be on standard therapy, including an ACE inhibitor (or ARB) and a β-blocker. • The triple combination of an ACE inhibitor, an ARB, and an aldosterone antagonist is not recommended because of the high risk of hyperkalemia. <u>Patients with hypertension and symptomatic left ventricular dysfunction with left ventricular dilation and low LVEF</u> • ACE inhibitors, ARBs, β-blockers, aldosterone inhibitors, and isosorbide dinitrate/hydralazine in various combinations (with a loop diuretic if needed) are

Clinical Guideline	Recommendation(s)
	recommended. • If blood pressure remains >130/80 mm Hg, a dihydropyridine calcium channel blocker (e.g., amlodipine or felodipine) may be considered or other antihypertensive medication doses increased. <u>Managing heart failure in special populations</u> • The combination of hydralazine/isosorbide dinitrate is recommended for African American women with moderate to severe heart failure symptoms who are on background neurohormonal inhibition. • A combination of hydralazine and isosorbide dinitrate is recommended as part of standard therapy in addition to β-blockers and ACE-inhibitors for African Americans with left ventricular systolic dysfunction and NYHA class II-IV heart failure. • As in all patients, but especially in the elderly, careful attention to volume status, the possibility of symptomatic cerebrovascular disease and the presence of postural hypotension are recommended during therapy with ACE inhibitors, β-blockers and diuretics. <u>Patients with heart failure and preserved LVEF</u> • ACE inhibitors or ARBs should be considered in this patient population. • ACE inhibitors should be considered in patients with heart failure and symptomatic atherosclerotic cardiovascular disease or diabetes and at least one other risk factor. ARBs may be used in patients who are intolerant to ACE inhibitors. • Beta-blocker treatment is recommended in patients with HF and preserved LVEF who have prior MI, hypertension, or AF. • Calcium channel blockers should be considered in patients with heart failure and preserved LVEF who have atrial fibrillation requiring ventricular rate control and intolerance to β-blockers (consider diltiazem or verapamil), symptom-limiting angina, or hypertension. • Diuretic therapy is recommended in all patients with heart failure and clinical evidence of volume overload, including those with preserved LVEF. • Treatment may begin with either a thiazide or loop diuretic. In more severe volume overload or if response to a thiazide is inadequate, treatment with a loop diuretic should be implemented. • Excessive diuresis, which may lead to orthostatic changes in blood pressure and worsening renal function, should be avoided. <u>Patients with heart failure and CAD</u> • Calcium channel blockers should be considered in patients who have angina despite optimization of β-blocker and nitrates. Amlodipine and felodipine are preferred in patients with decreased systolic function. <u>Patients with heart failure and hypertension</u> • Patients with left ventricular hypertrophy or left ventricular dysfunction without left ventricular dilation should be treated to a goal blood pressure of <130/80 mm Hg. Treatment with several drugs may be necessary, including an ACE inhibitor (or ARB), a diuretic and a β-blocker or calcium channel blocker. • Patients with asymptomatic left ventricular dysfunction and left ventricular dilation and a reduced ejection fraction should receive an ACE inhibitor and a β-blocker. If blood pressure remains elevated (>130/80 mm Hg), the addition of a diuretic is recommended, followed by a calcium channel blocker or other antihypertensive agent. • If blood pressure remains >130/80 mm Hg, then the addition of a thiazide diuretic is recommended, followed by a dihydropyridine calcium channel blocker (e.g.,

Clinical Guideline	Recommendation(s)
	amlodipine or felodipine) or other antihypertensive drugs. <u>Patients at risk for development of heart failure</u> • ACE inhibitors are recommended in patients who are at risk for the development of heart failure including patients with CAD, peripheral vascular disease, stroke, diabetes and another major risk factor, and patients with diabetes who smoke and have microalbuminuria. <u>Patients with asymptomatic heart failure and reduced LVEF</u> • ACE inhibitors are recommended in asymptomatic patients with reduced LVEF (<40%). • ARBs may be used in patients who are intolerant to ACE inhibitors. • Routine use of a combination of ACE inhibitors and ARBs is not recommended. • β-blocker therapy should be considered. <u>Patients with heart failure and ischemic heart disease</u> • ACE inhibitor therapy is recommended in all patients with either reduced or preserved LVEF after a MI. • Beta-blockers are recommended for the management of all patients with reduced LVEF or post-MI. • ACE inhibitor and β-blocker therapy should be initiated early (<48 hours) during hospitalization in hemodynamically stable patients who are post-MI with reduced LVEF or heart failure. • Calcium channel blockers may be considered in patients with HF who have angina despite the optimal use of β-blockers and nitrates. <u>Managing heart failure in the elderly, women and African Americans</u> • Standard regimens of ACE inhibitors and β-blockers are recommended in elderly patients with heart failure. • ACE inhibitor and β-blocker therapy are recommended in all women with heart failure and left ventricular systolic dysfunction. • ACE inhibitor and β-blocker therapy are recommended in all African American patients with heart failure and left ventricular systolic dysfunction. ARBs may be substituted in patients who are intolerant to ACE inhibitors. <u>Heart failure in patients with reduced ejection fraction</u> • ACE inhibitors are recommended in asymptomatic patients with reduced LVEF (<40%). • ARBs may be used in patients who are intolerant to ACE inhibitors. • β-blockers shown to be effective in clinical trials of patients with heart failure are recommended for patients with a LVEF ≤40%. • The combination of a β-blocker and an ACE inhibitor is recommended as routine therapy for asymptomatic patients with a LVEF ≤40%. The evidence is stronger in patients with a history of MI. • β-blocker therapy is recommended for patients with a recent decompensation of heart failure after optimization of volume status and successful discontinuation of intravenous diuretics and vasoactive drugs. Whenever possible, β-blocker therapy should be initiated in the hospital setting at a low dose prior to discharge of stable patients. • β-blocker therapy is recommended in the great majority of patients with heart failure and reduced LVEF, even if there is concurrent diabetes, chronic obstructive pulmonary disease or peripheral vascular disease. Caution may be warranted in these patients. • It is recommended that β blockade be initiated at low doses and uptitrated gradually.

Clinical Guideline	Recommendation(s)
	• It is recommended that β-blocker therapy be continued in most patients experiencing a symptomatic exacerbation of heart failure during chronic maintenance treatment, unless they develop cardiogenic shock, refractory volume overload or symptomatic bradycardia. • The routine use of an ARB is not recommended in addition to an ACE inhibitor and a β-blocker in patients with a recent acute MI and reduced LVEF. • The addition of an ARB should be considered in patients with heart failure due to reduced LVEF who have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor and a β-blocker. • Administration of an aldosterone antagonist is recommended for patients with NYHA class IV (or class III, previously class IV) HF from reduced LVEF (<35%) while receiving standard therapy, including diuretics. • Diuretic therapy is recommended to restore and maintain normal volume status in patients with clinical evidence of fluid overload, generally manifested by congestive symptoms or signs of elevated filling pressures. Loop diuretics rather than thiazide-type diuretics are typically necessary to restore normal volume status in patients with heart failure. • The initial dose of diuretic may be increased as necessary to relieve congestion, and restoration of normal volume status may require multiple adjustments, especially in patients with severe fluid overload evidenced by massive edema or ascites. After a diuretic effect is achieved with loop diuretics (short acting), increasing administration frequency to twice or even three times/day will provide more diuresis with less physiologic perturbation than larger single doses. • Oral torsemide may be considered in patients in whom poor absorption of oral medication or erratic diuretic effect may be present. Particularly in patients with right-sided heart failure and refractory fluid retention despite high doses of other loop diuretics. • Intravenous administration of diuretics may be necessary to relieve congestion. • Diuretic refractoriness may represent patient nonadherence, a direct effect of diuretic use on the kidney or progression of underlying cardiac dysfunction. • Addition of chlorothiazide or metolazone, once or twice daily, to loop diuretics should be considered in patients with persistent fluid retention despite high dose loop diuretic therapy. Chronic daily use should be avoided if possible because of the potential for electrolyte shifts and volume depletion. These drugs may be used periodically (every other day or weekly) to optimize fluid management. Metolazone will generally be more potent and much longer acting in this setting and in patients with chronic renal insufficiency, so administration should be adjusted accordingly. Volume status and electrolytes must be monitored closely when multiple diuretics are used. • Careful observation for the development of side effects is recommended in patients treated with diuretics, especially when high doses or combination therapy are used. Patients should undergo routine laboratory studies and clinical examination as dictated by their clinical response. • Patients requiring diuretic therapy to treated fluid retention associated with heart failure generally require chronic treatment, although often at lower doses than those required initially to achieve diuresis. Decreasing or discontinuing therapy may be considered in patients experiencing significant improvement in clinical status and cardiac function or in those who successfully restrict dietary sodium intake. These patients may undergo cautious weaning of diuretic dose and frequency with careful observation for recurrent fluid retention. • Patients and caregivers should be given education on the early signs of fluid retention and the plan for initial therapy. • Selected patients may be educated to adjust daily dose of diuretic in response to weight gain from fluid overload.

Clinical Guideline	Recommendation(s)

	Evaluation and management of patients with acute decompensated heart failure
	• Patients admitted with acute decompensated heart failure and evidence of fluid overload be treated initially with loop diuretics; usually given intravenously rather than orally. Ultrafiltration may be considered in lieu of diuretics.
	• Diuretics should be administered at doses needed to produce a rate of diuresis sufficient to achieve optimal volume status with relief of signs and symptoms of congestion, without inducing an excessively rapid reduction in intravascular volume or serum electrolytes.
	• Monitoring of daily weights, intake and output is recommended to assess clinical efficacy of diuretic therapy.
	• Careful observation for development of a variety of side effects, including renal dysfunction, electrolyte abnormalities, symptomatic hypotension and gout is recommended in patients treated with diuretics, especially when high doses or combination therapy is used.
	• Careful observation for the development of renal dysfunction is recommended in patients treated with diuretics. Patients with moderate to severe renal dysfunction and evidence of fluid retention should continue to be treated with diuretics. In the presence of severe fluid overload, renal dysfunction may improve with diuresis.
	• When congestion fails to improve in response to diuretic therapy, the following options should be considered:
	  ○ Re-evaluating the presence/absence of congestion.
	  ○ Sodium and fluid restriction.
	  ○ Increasing doses of loop diuretic.
	  ○ Continuous infusion of a loop diuretic.
	  ○ Addition of a second type of diuretic orally (metolazone or spironolactone) or intravenously (chlorothiazide).
	  ○ Ultrafiltration may be considered as well.

European Society of Cardiology: **Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (2016)**[7]	Pharmacological treatments indicated in patients with symptomatic (NYHA Class II-IV) heart failure with reduced ejection fraction • An ACE inhibitor is recommended, in addition to a beat-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death. • A mineralocorticoid receptor antagonist 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. • Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion. • 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. • 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

Clinical Guideline	Recommendation(s)
	patients who are symptomatic despite treatment with a β-blocker who are unable to tolerate a mineralocorticoid receptor antagonist. • 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 heart failure with preserved ejection fraction and heart failure with mid-range ejection fraction</u> • It is recommended to screen patients with HFpEF or HFmrEF (mid-range) 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 or HFmrEF in order to alleviate symptoms and signs. <u>Recommendations for initial management of a rapid ventricular rate in patients with heart failure and atrial fibrillation in the acute or chronic setting</u> • Urgent electrical cardioversion is recommended if AF is thought to be contributing to the patient's hemodynamic compromise in order to improve the patient clinical condition. • For patients in NYHA Class IV, in addition to treatment for acute HF, an intravenous bolus of amiodarone or, in digoxin-naïve patients, an intravenous bolus of digoxin should be considered to reduce the ventricular rate. • For patients in NYHA Class I–III, a β-blocker, usually given orally, is safe and therefore is recommended as first-line treatment to control ventricular rate, provided the patient is euvolemic. • For patients in NYHA Class I–III, digoxin should be considered when ventricular rate remains high despite β-blockers or when β-blockers are not tolerated or contraindicated. • Treatment with dronedarone to improve ventricular rate control is not recommended due to safety concerns. <u>Recommendations for cardiac imaging in patients with suspected or established heart failure</u> • Transthoracic Echocardiogram (TTE) is recommended for the assessment of myocardial structure and function in subjects with suspected HF in order to establish a diagnosis of HFrEF, HFmrEF, or HFpEF. • TTE is recommended for the assessment of LVEF in order to identify patients with HF who would be suitable for evidence-based pharmacological and device treatment recommended for HFrEF. <u>Recommendations aiming to prevent or delay the development of overt heart failure or prevent death before the onset of symptoms</u> • Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life. • ACE inhibitor is recommended in patients with asymptomatic LV systolic

Clinical Guideline	Recommendation(s)
	dysfunction and a history of myocardial infarction in order to prevent or delay the onset of HF and prolong life. • Beta-blocker is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction, in order to prevent or delay the onset of HF and prolong life. Pharmacological treatments indicated in patients with symptomatic 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 β-blocker is recommended, in addition to an ACE inhibitor, for patients with stable, symptomatic HFrEF to reduce the risk of HF hospitalization and death. • A mineralocorticoid receptor antagonist 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. Other pharmacological treatments recommended in selected patients with symptomatic heart failure with reduced ejection fraction • Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion. • 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. Treatments (or combinations of treatments) that may cause harm in patients with symptomatic (New York Heart Association Class II–IV) heart failure with reduced ejection fraction • Diltiazem or verapamil are not recommended in patients with HFrEF, as they increase the risk of HF worsening and HF hospitalization. • The addition of an ARB (or a renin inhibitor) to the combination of an ACE inhibitor and a mineralocorticoid receptor antagonist is not recommended in patients with HF, because of the increased risk of renal dysfunction and hyperkalemia. Not-recommended treatments of co-morbidities in patients with heart failure • Thiazolidinediones (glitazones) are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization. • NSAIDs or COX-2 inhibitors are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization. Recommendations for the 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. • In patients with new-onset AHF or those with chronic, decompensated HF not receiving oral diuretics the initial recommended dose should be 20 to 40 mg intravenous furosemide (or equivalent); for those on chronic diuretic therapy, initial intravenous dose should be at least equivalent to oral dose. • It is recommended to give diuretics either as intermittent boluses or a continuous infusion, and the dose and duration should be adjusted according to the patients' symptoms and clinical status. • Inotropic agents are not recommended unless the patient is symptomatically

Clinical Guideline	Recommendation(s)
	hypotensive or hypoperfused because of safety concern.
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 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.
American Society of Hypertension/ International Society of Hypertension: **Clinical Practice Guidelines for the Management of Hypertension in the Community (2014)**[9]	Nonpharmacologic treatment • In patients with hypertension that is no more severe than stage one and is not associated with evidence of abnormal cardiovascular findings or other cardiovascular risks, six to 12 months of lifestyle changes can be attempted in the hope that they may be sufficiently effective to make it unnecessary to use medicines. • It may be prudent to start treatment with drugs sooner if it is clear that the blood pressure is not responding to the lifestyle methods or if other risk factors appear. • Weight loss: In patients who are overweight or obese, weight loss is helpful in treating hypertension, diabetes, and lipid disorders. • Salt reduction: Reduction of salt intake is recommended because it can reduce blood pressure and decrease the need for medications in patients who are "salt sensitive." • Exercise: Regular aerobic exercise can help reduce blood pressure. • Alcohol consumption: Up to two drinks a day can be helpful in protecting against cardiovascular events, but greater amounts of alcohol can raise blood pressure and

Clinical Guideline	Recommendation(s)

	should therefore be discouraged. In women, alcohol should be limited to one drink a day.
	• Cigarette smoking: Stopping smoking will not reduce blood pressure, but since smoking by itself is such a major cardiovascular risk factor, patients must be strongly urged to discontinue this habit.
	
	<u>Drug treatment of hypertension</u>
	• Treatment with drugs should be started in patients with blood pressures >140/90 mm Hg in whom lifestyle treatments have not been effective.
	• In patients with stage two hypertension (blood pressure ≥160/100 mm Hg), drug treatment should be started immediately after diagnosis, usually with a two-drug combination, without waiting to see the effects of lifestyle changes.
	• For patients older than 80 years, the suggested threshold for starting treatment is at levels ≥150/90 mm Hg. Thus, the target of treatment should be <140/90 mm Hg for most patients but <150/90 mm Hg for older patients (unless these patients have chronic kidney disease or diabetes, when <140/90 mm Hg can be considered).
	• Most patients will require more than one drug to achieve control of their blood pressure.
	• In general, increase the dose of drugs or add new drugs at approximately two to three week intervals. This frequency can be faster or slower depending on the judgment of the practitioner. In general, the initial doses of drugs chosen should be at least half of the maximum dose so that only one dose adjustment is required thereafter. It is generally anticipated that most patients should reach an effective treatment regimen, whether one, two, or three drugs, within six to eight weeks.
	• Choice of drugs should be influenced by the age, ethnicity/race, and other clinical characteristics of the patient.
	• The choice of drugs will also be influenced by other conditions (e.g., diabetes and coronary disease) associated with the hypertension. Pregnancy also influences drug choice.
	• Long-acting drugs that need to be taken only once daily are preferred to shorter-acting drugs that require multiple doses because patients are more likely to follow a simple treatment regimen.
	• This guideline only makes recommendations for drug classes, not individual agents. There is an assumption, unless otherwise stated, that all drugs in a class are similar to each other.
	• Drug selectin when hypertension is the only or main concern:
	  ○ For black patients of all ages, use calcium channel blocker (CCB) or thiazide diuretic as first drug, then add angiotensin receptor blocker (ARB) or angiotensin-converting enzyme (ACE) inhibitor if needed.
	  ○ For white and other non-black patients <60 years of age, use ARB or ACE inhibitor as first drug, then add CCB or thiazide diuretic if needed.
	  ○ For white and other non-black patients ≥60 years of age, use CCB or thiazide diuretic as first drug, then add ARB or ACE inhibitor if needed.
	• Drug selection when hypertension is associated with other conditions:
	  ○ For patients with hypertension and diabetes, use ARB or ACE inhibitor as first drug (note, in black patients it is acceptable to start with a CCB or thiazide), then add CCB or thiazide diuretic (unless starting on CCB or thiazide in black patients) if needed.
	  ○ For patients with hypertension and chronic kidney disease, use ARB or ACE inhibitor as first drug, then add CCB or thiazide diuretic if needed.
	  ○ For patients with hypertension and clinical coronary artery disease, use β-blocker plus ARB or ACE inhibitor as first drugs, then add CCB or thiazide diuretic if needed.
	  ○ For patients with hypertension and stroke history, use ACE inhibitor or ARB as first drug, then add thiazide diuretic or CCB if needed.

Clinical Guideline	Recommendation(s)
	• For patients with hypertension and heart failure, patients with h symptomatic heart failure should usually receive an ARB or ACE inhibitor plus β-blocker plus diuretic plus spironolactone regardless of blood pressure. A dihydropyridine CCB can be added if needed for blood pressure control.

Hypertension Canada: **2017 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults (2017)**[10]	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.
	
	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.
	
	Guidelines for individuals 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.
	
	Treatment of hypertension in association with stroke
	• BP management in acute ischemic stroke (onset to 72 hours)
	  ○ For patients with ischemic stroke not eligible for thrombolytic therapy, treatment of hypertension in the setting of acute ischemic stroke or transient ischemic attack should not be routinely undertaken. Extreme BP increases (e.g., SBP >220 mmHg or DBP >120 mmHg) may be treated to reduce the BP by approximately 15%, and not more than 25%, over the first 24 hours with gradual reduction thereafter. Avoid excessive lowering of BP because this might exacerbate existing ischemia or might induce ischemia, particularly in the setting of intracranial arterial occlusion or extracranial carotid or vertebral artery occlusion. Pharmacological agents and routes of administration should be chosen to avoid precipitous decreases in BP.
	  ○ For patients with ischemic stroke eligible for thrombolytic therapy, very high BP (>185/110 mmHg) should be treated concurrently in patients receiving thrombolytic therapy for acute ischemic stroke to reduce the risk of secondary intracranial hemorrhage.
	• 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)
	  ○ For patients with intracerebral hemorrhage (ICH) in the hyperacute phase (in the first 24 hours) SBP lowering to <140 mmHg should be avoided because of an absence of benefit (relative to a target of <180 mmHg) and some suggestion of harm.
	
	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
	• For patients with nondiabetic chronic kidney disease, target BP is <140/90 mmHg.
	• For patients with hypertension and proteinuric chronic kidney disease (urinary protein >500 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.
	• Thiazide/thiazide-like diuretics are recommended as additive antihypertensive therapy. For patients with chronic kidney disease and volume overload, loop diuretics are an alternative.
	• 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.

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	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. • In patients with hypertension attributable to FMD-related renal artery stenosis, revascularization should be considered. • 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 2 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. Combination therapy using two first-line agents may also be considered as initial treatment of hypertension if SBP is 20 mmHg greater than target or if DBP is 10 mmHg greater than target. However, caution should be exercised in patients in whom a substantial decrease in BP is more likely or poorly tolerated (e.g., elderly patients and patients with autonomic neuropathy). • 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.
European Society of Hypertension/ European Society of Cardiology: **2013 Guidelines for the management of arterial hypertension (2013)**[11]	The 2013 guidelines on hypertension of the European Society of Hypertension and the European Society of Cardiology follow the guidelines jointly issued by the two societies in 2003 and 2007. Treatment strategies and choice of antihypertensive drugs • Diuretics (including thiazides, chlorthalidone, and indapamide), β-blockers, calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) are all suitable for the initiation and maintenance of antihypertensive treatment, either as monotherapy or in some combinations. • Some agents should be considered as the preferential choice in specific conditions because used in trials in those conditions or because of greater effectiveness in specific types of organ damage. • Initiation of antihypertensive therapy with a two-drug combination may be considered in patients with markedly high baseline blood pressure (BP) or at high cardiovascular (CV) risk. • The combination of two antagonists of the renin-angiotensin system (RAS) is not recommended and should be discouraged. • Other drug combinations should be considered and probably are beneficial in proportion to the extent of BP reduction. However, combinations that have been

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	successfully used in trials may be preferable. • Combinations of two antihypertensive drugs at fixed doses in a single tablet may be recommended and favored, because reducing the number of daily pills improves adherence, which is low in patients with hypertension. <u>Treatment strategies in white-coat and masked hypertension</u> • In white-coat hypertensives without additional risk factors, therapeutic intervention may be limited to lifestyle changes only, but this decision should be accompanied by close follow-up. • In white-coat hypertensives with a higher CV risk because of metabolic derangements or asymptomatic organ damage, drug treatment may be considered in addition to lifestyle changes. • In masked hypertension, both lifestyle measures and antihypertensive drug treatment should be considered, because this type of hypertension has been consistently found to have a CV risk very close to that of in- and out-of-office hypertension. <u>Antihypertensive treatment strategies in the elderly</u> • In elderly hypertensives with SBP ≥160 mmHg there is solid evidence to recommend reducing SBP to between 150 and 140 mmHg. • In fit elderly patients <80 years old antihypertensive treatment may be considered at SBP values ≥140 mmHg with a target SBP <140 mmHg if treatment is well tolerated. • In individuals older than 80 years with an initial SBP ≥160 mmHg, it is recommended to reduce SBP to between 150 and 140 mmHg, provided they are in good physical and mental conditions. • In frail elderly patients, it is recommended to leave decisions on antihypertensive therapy to the treating physician, and based on monitoring of the clinical effects of treatment. • Continuation of well-tolerated antihypertensive treatment should be considered when a treated individual becomes an octogenarian. • All hypertensive agents are recommended and can be used in the elderly, although diuretics and calcium antagonists may be preferred in isolated systolic hypertension. <u>Treatment strategies in hypertensive women</u> • Hormone therapy and selective estrogen receptor modulators are not recommended and should not be used for primary or secondary prevention of CVD. • If treatment of younger perimenopausal women is considered for severe menopausal symptoms, the benefits should be weighed against potential risks. • Drug treatment of severe hypertension in pregnancy (SBP >160 mmHg or DBP >110 mmHg) is recommended. • Drug treatment may also be considered in pregnant women with persistent elevation of BP ≥150/95 mmHg, and in those with BP ≥140/90 mmHg in the presence of gestational hypertension, subclinical organ damage or symptoms. • In women at high risk of pre-eclampsia, provided they are at low risk of gastrointestinal hemorrhage, treatment with low dose aspirin from 12 weeks until delivery may be considered. • In women with child-bearing potential RAS blockers are not recommended and should be avoided. • Methyldopa, labetalol, and nifedipine should be considered preferential antihypertensive drugs in pregnancy. Intravenous labetalol or infusion of nitroprusside should be considered in case of emergency (pre-eclampsia).

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	Treatment strategies in patients with diabetes • While initiation of antihypertensive drug treatment in diabetic patients whose SBP is ≥160 mmHg is mandatory, it is strongly recommended to start drug treatment also when SBP is ≥140 mmHg. • A SBP goal <140 mmHg is recommended in patients with diabetes. • The DBP target in patients with diabetes is recommended to be <85 mmHg. • All classes of antihypertensive agents are recommended and can be used in patients with diabetes; RAS blockers may be preferred, especially in the presence of proteinuria or microalbuminuria. • It is recommended that individual drug choice takes comorbidities into account. • Simultaneous administration of two blockers of the RAS is not recommended and should be avoided in patients with diabetes Treatment strategies in hypertensive patients with metabolic syndrome • Lifestyle changes, particularly weight loss and physical exercise, are to be recommended to all individuals with the metabolic syndrome. These interventions improve not only BP, but the metabolic components of the syndrome and delay diabetes onset. • As the metabolic syndrome can be considered a 'pre-diabetic' state, antihypertensive agents potentially improving or at least not worsening insulin sensitivity, such as RAS blockers and calcium antagonists, should be considered as the preferred drugs. Beta-blockers (with the exception of vasodilating β-blockers) and diuretics should be considered only as additional drugs, preferably in association with a potassium-sparing agent. • It is recommended to prescribe antihypertensive drugs with particular care in hypertensive patients with metabolic disturbances when BP is ≥140/90 mmHg after a suitable period of lifestyle changes, and to maintain BP <140/90 mmHg. • BP lowering drugs are not recommended in individuals with metabolic syndrome and high normal BP. Therapeutic strategies in hypertensive patients with nephropathy • Lowering SBP to <140 mmHg should be considered. • When overt proteinuria is present, SBP values <130 mmHg may be considered, provided that changes in eGFR are monitored. • RAS blockers are more effective in reducing albuminuria than other antihypertensive agents, and are indicated in hypertensive patients in the presence of microalbuminuria or overt proteinuria. • Reaching BP goals usually requires combination therapy, and it is recommended to combine RAS blockers with other antihypertensive agents. • Combination of two RAS blockers, though potentially more effective in reducing proteinuria, is not recommended. • Aldosterone antagonists cannot be recommended in chronic kidney disease (CKD), especially in combination with a RAS blocker, because of the risk of excessive reduction in renal function and of hyperkalemia. Therapeutic strategies in hypertensive patients with cerebrovascular disease • It is not recommended to intervene with BP-lowering therapy during the first week after acute stroke irrespective of BP level, although clinical judgement should be used in the face of very high SBP values. • Antihypertensive treatment is recommended in hypertensive patients with a history of stroke or transient ischemic attack (TIA), even when initial SBP is in the 140 to 159 mmHg range. • In hypertensive patients with a history of stroke or TIA, a SBP goal of <140 mmHg should be considered. • In elderly hypertensives with previous stroke or TIA, SBP values for intervention

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	and goal may be considered to be somewhat higher. • All drug regimens are recommended for stroke prevention, provided that BP is effectively reduced. <u>Therapeutic strategies in hypertensive patients with heart disease</u> • In hypertensive patients with CHD, a SBP goal <140 mmHg should be considered. • In hypertensive patients with a recent myocardial infarction, β-blockers are recommended. In case of other CHD all antihypertensive agents can be used, but β-blockers and calcium antagonists are to be preferred for symptomatic reasons (angina). • Diuretics, β-blockers, ACE inhibitors, angiotensin receptor blockers, and/or mineralocorticoid receptor antagonists are recommended in patients with heart failure or severe left ventricular (LV) dysfunction to reduce mortality and hospitalization. • In patients with heart failure and preserved ejection fraction (EF), there is no evidence that antihypertensive therapy per se or any particular drug is beneficial. However, in these patients, as well as in patients with hypertension and systolic dysfunction, lowering SBP to around 140 mmHg should be considered. Treatment guided by relief of symptoms (congestion with diuretics, high heart rate with β-blockers, etc.) should also be considered. • ACE inhibitors and angiotensin receptor blockers (and β-blockers and mineralocorticoid receptor antagonists if heart failure coexists) should be considered as antihypertensive agents in patients at risk of new or recurrent atrial fibrillation. • It is recommended that all patients with left ventricular hypertrophy (LVH) receive antihypertensive agents. • In patients with LVH, initiation of treatment with one of the agents that have shown a greater ability to regress LVH should be considered, i.e. ACE inhibitors, angiotensin receptor blockers, and calcium antagonists. <u>Therapeutic strategies in hypertensive patients with atherosclerosis, arteriosclerosis, and peripheral artery disease (PAD)</u> • In the presence of carotid atherosclerosis, prescription of calcium antagonists and ACE inhibitors should be considered as these agents have shown a greater efficacy in delaying atherosclerosis progression than diuretics and β-blockers. • In hypertensive patients with a pulse wave velocity above 10 m/s, all antihypertensive drugs should be considered provided that a BP reduction to <140/90 mmHg is consistently achieved. • Antihypertensive therapy is recommended in hypertensive patients with PAD to achieve a goal of <140/90 mmHg, because of their high risk of myocardial infarction, stroke, heart failure, and CV death. • Though a careful follow up is necessary, β-blockers may be considered for the treatment of arterial hypertension in patients with PAD, since their use does not appear to be associated with exacerbation of PAD symptoms.
National Institute for Health and Clinical Excellence: **Hypertension in adults: diagnosis and management (2011)**[12] **Reaffirmed Nov 2016**	<u>Choosing antihypertensive drug treatment</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 people ≥80 years of age the same antihypertensive drug treatment as people aged 55 to 80 years, taking into account any comorbidities. • Offer antihypertensive drug treatment to women of child-bearing potential in line with the recommendations on Management of pregnancy with chronic hypertension and Breastfeeding in 'Hypertension in pregnancy' (NICE clinical

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	guideline 107).
	
	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). 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 step one antihypertensive (ACE inhibitor, ARB) with a calcium channel blocker (CCB) to patients >55 years of age and to black patients of African or Caribbean family origin 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 chlorthalidone (12.5 to 25.0 mg once daily) or indapamide (1.5 mg modified-release once daily or 2.5 mg once daily) in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide.
	• For patients who are already receiving treatment with bendroflumethiazide or hydrochlorothiazide and whose blood pressure is stable and well controlled, continue treatment as is.
	• β-blockers are not a preferred initial therapy for hypertension; however, β-blockers may be considered in younger patients, particularly:
	  ○ Patients with an intolerance or contraindication to ACE inhibitors and ARBs.
	  ○ Women of child-bearing potential.
	  ○ People with evidence of increased sympathetic drive.
	• If treatment is initiated with a β-blocker and a second antihypertensive is required, add a CCB over a thiazide-like diuretic to reduce the risk of developing diabetes.
	
	Step two treatment
	• If blood pressure is not controlled with a step one antihypertensive, offer a step two treatment with a CCB in combination with an ACE inhibitor or an ARB.
	• If a CCB is not appropriate or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic.
	• For black patients of African or Caribbean family origin, consider an ARB in preference to an ACE inhibitor, in combination with a CCB.
	
	Step three treatment
	• Before considering step three treatment, review medication to ensure step two treatment is at optimal or best tolerated doses.
	• If three drugs are required to control blood pressure, the combination of an ACE inhibitor or ARB, CCB, and thiazide-like diuretic should be utilized.
	
	Step four treatment
	• Regard clinic blood pressure that remains >140/90 mmHg after treatment with the optimal or best tolerated doses of an ACE inhibitor or an ARB plus a CCB plus a diuretic as resistant hypertension, and consider adding a fourth antihypertensive drug and/or seeking expert advice.
	• For treatment of resistant hypertension at step four:
	  ○ Consider further diuretic therapy with low-dose spironolactone (25 mg once daily) if the blood potassium level is 4.5 mmol/l or lower. Use particular caution in people with a reduced estimated glomerular filtration rate because they have an increased risk of hyperkalemia.
	  ○ Consider higher-dose thiazide-like diuretic treatment if the blood potassium level is higher than 4.5 mmol/l.
	  ○ If further diuretic therapy for resistant hypertension is not tolerated or is

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	contraindicated or ineffective, consider an α-blocker or β-blocker.
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 (2012)**[14]	<u>Blood pressure management in chronic kidney disease (CKD) non-dialysis (ND) patients without diabetes mellitus</u> • The Work Group recommends that non-diabetic adults with CKD ND and urine albumin excretion <30 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >140 mm Hg systolic or >90 mm Hg diastolic be treated with blood pressure -lowering drugs to maintain a blood pressure that is consistently ≤140 mm Hg systolic and ≤90 mm Hg diastolic. • The Work Group suggests that non-diabetic adults with CKD ND and urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with BP-lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic. • The Work Group suggests that non-diabetic adults with CKD ND and urine albumin excretion >300 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with blood pressure -lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤ 80 mm Hg diastolic. • The Work Group suggests that an angiotensin receptor blocker (ARB) or angiotensin converting enzyme inhibitor (ACE-I) be used in non-diabetic adults with CKD ND and urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*) in whom treatment with blood pressure -lowering drugs is indicated. • The Work Group recommends that an ARB or ACE-I be used in non-diabetic adults with CKD ND and urine albumin excretion >300 mg per 24 hours (or equivalent*) in whom treatment with blood pressure -lowering drugs is indicated. <u>Blood pressure management in CKD ND patients with diabetes mellitus</u> • The Work Group recommends that adults with diabetes and CKD ND with urine albumin excretion <30 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >140 mm Hg systolic or >90 mm Hg diastolic be treated with BP-lowering drugs to maintain a blood pressure that is consistently ≤140 mm Hg systolic and ≤90 mm Hg diastolic.

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	• The Work Group suggests that adults with diabetes and CKD ND with urine albumin excretion >30 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with BP-lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic. • The Work Group suggests that an ARB or ACE-I be used in adults with diabetes and CKD ND with urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*). • The Work Group recommends that an ARB or ACE-I be used in adults with diabetes and CKD ND with urine albumin excretion >300 mg per 24 hours (or equivalent*). <u>Blood pressure management in kidney transplant recipients (non–dialysis-dependent CKD of any stage with a kidney transplant [CKD T])</u> • The Work Group suggests that adult kidney transplant recipients whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic, irrespective of the level of urine albumin excretion. • In adult kidney transplant recipients, choose a blood pressure -lowering agent after taking into account the time after transplantation, use of calcineurin inhibitors, presence or absence of persistent albuminuria, and other co morbid conditions. <u>Blood pressure management in children with CKD ND</u> • The Work Group recommends that in children with CKD ND, blood pressure -lowering treatment is started when blood pressure is consistently above the 90th percentile for age, sex, and height. • The Work Group suggests that in children with CKD ND (particularly those with proteinuria), blood pressure is lowered to consistently achieve systolic and diastolic readings less than or equal to the 50th percentile for age, sex, and height, unless achieving these targets is limited by signs or symptoms of hypotension. • The Work Group suggests that an ARB or ACE-I be used in children with CKD ND in whom treatment with blood pressure -lowering drugs is indicated, irrespective of the level of proteinuria. <u>Blood pressure management in elderly persons with CKD ND</u> • Tailor blood pressure treatment regimens in elderly patients with CKD ND by carefully considering age, co-morbidities and other therapies, with gradual escalation of treatment and close attention to adverse events related to blood pressure treatment, including electrolyte disorders, acute deterioration in kidney function, orthostatic hypotension and drug side effects. *Approximate equivalents for albumin excretion rate per 24 hours is expressed as protein excretion rate per 24 hours, albumin/creatinine ratio, protein/creatinine ratio, and protein reagent strip results.
American Diabetes Association: **Standards of Medical Care in Diabetes (2017)**[15]	<u>Hypertension/blood pressure control</u> • Blood pressure should be measured at every routine visit. Patients found to have elevated blood pressure should have blood pressure confirmed on a separate day. • Most patients with diabetes and hypertension should be treated to a systolic blood pressure goal of <140 mmHg and a diastolic blood pressure goal of <90 mmHg. • Lower systolic and diastolic blood pressure targets, such as 130/80 mmHg, may be appropriate for individuals at high risk of cardiovascular disease, if they can be achieved without undue treatment burden. • In pregnant patients with diabetes and chronic hypertension, blood pressure targets of 120 to 160/80 to 105 mmHg are suggested in the interest of optimizing long-term maternal health and minimizing impaired fetal growth.

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	• Patients with confirmed office-based blood pressure >140/90 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). 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. • For patients with blood pressure >120/80 mmHg, lifestyle intervention consists of weight loss if overweight or obese; a Dietary Approaches to Stop Hypertension–style dietary pattern including reducing sodium and increasing potassium intake; moderation of alcohol intake; and increased physical activity. <u>Coronary heart disease</u> • In asymptomatic patients, routine screening for coronary artery disease is not recommended as it does not improve outcomes as long as atherosclerotic cardiovascular disease risk factors are treated. • Consider investigations for coronary artery disease in the presence of any of the following: atypical cardiac symptoms (e.g., unexplained dyspnea, chest discomfort); signs or symptoms of associated vascular disease including carotid bruits, transient ischemic attack, stroke, claudication, or peripheral arterial disease; or electrocardiogram abnormalities (e.g., Q waves). • In patients with known atherosclerotic cardiovascular disease, use aspirin and statin therapy (if not contraindicated) and consider ACE inhibitor therapy to reduce the risk of cardiovascular events. • In patients with prior myocardial infarction, β-blockers should be continued for at least two years after the event. • In patients with symptomatic heart failure, thiazolidinedione treatment should not be used. • In patients with type 2 diabetes with stable congestive heart failure, metformin may be used if estimated glomerular filtration remains >30 mL/min but should be avoided in unstable or hospitalized patients with congestive heart failure. <u>Diabetic 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, in all patients with type 2 diabetes, and in all patients with comorbid hypertension. • Optimize glucose control to reduce the risk or slow the progression of diabetic kidney disease. • Optimize blood pressure control to reduce the risk or slow the progression of diabetic kidney disease.

Clinical Guideline	Recommendation(s)
	• For people with nondialysis-dependent diabetic kidney disease, dietary protein intake should be approximately 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. • 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) B 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 or changes in potassium when ACE inhibitors, angiotensin receptor blockers, or diuretics are used. • Continued monitoring of urinary albumin–to–creatinine ratio in patients with albuminuria treated with an ACE inhibitor or an angiotensin receptor blocker is reasonable to assess the response to treatment and progression of diabetic kidney disease. • An ACE inhibitor or an angiotensin receptor blocker is not recommended for the primary prevention of diabetic kidney disease 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. • When estimated glomerular filtration rate is <60 mL/min/1.73 m^2, evaluate and manage potential complications of chronic kidney disease. • Patients should be referred for evaluation for renal replacement treatment if they have an estimated glomerular filtration rate <30 mL/min/1.73 m^2. • Promptly refer to a physician experienced in the care of kidney disease for uncertainty about the etiology of kidney disease, difficult management issues, and rapidly progressing kidney disease.
American Association for the Study of Liver Diseases: **Management of Adult Patients with Ascites Due to Cirrhosis: Update 2012 (2012)**[16] **[Reaffirmed Oct 2014]**	Treatment of ascites • First line treatment of patients with cirrhosis and ascites consists of sodium restriction (88 mmol/day [2,000 mg/day]) and diuretics (oral spironolactone with or without oral furosemide). • Fluid restriction is not necessary unless serum sodium is <125 mmol/L. • Vasopressin antagonists may improve serum sodium in patients with cirrhosis and ascites. However their use does not currently appear justified in view of their expense, potential risks, and lack of evidence of efficacy in clinically meaningful outcomes. • An initial therapeutic abdominal paracentesis should be performed in patients with tense ascites. Sodium restriction and oral diuretics should then be initiated. • Diuretic-sensitive patients should preferably be treated with sodium restriction and oral diuretics rather than with serial paracentesis. • Use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers in patients with cirrhosis and ascites may be harmful and must be carefully considered in each patient, monitoring blood pressure and renal function. • The use of nonsteroidal anti-inflammatory drugs should be avoided in patients with cirrhosis and ascites, except in special circumstances. • Liver transplantation should be considered in patients with cirrhosis and ascites.

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 89
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

Generic Name(s)	Interaction	Mechanism
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. The boxed warning for metolazone is listed in Table 7.

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	-	-	✔
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	✔	-	✔

Adverse Event(s)	Chlorthalidone	Indapamide	Metolazone
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	✔	-	✔
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	-	-	✔

Adverse Event(s)	Chlorthalidone	Indapamide	Metolazone
Conjunctivitis	-	<5	-
Gout	-	-	✔
Hemoconcentration	-	-	✔
Hepatitis	-	-	✔
Infection	-	≥5	-
Jaundice	✔	-	✔
Necrotizing angiitis/vasculitis	-	-	✔
Vasculitis	✔	<5	-
Weight loss	-	<5	-

✔ Percent not specified
- Event not reported

Table 7. Boxed Warning for Metolazone[1]

WARNING
Do not interchange Zaroxolyn® tablets and other formulations of metolazone that share its slow and incomplete bioavailability and are not therapeutically equivalent at the same doses to Mykrox®* tablets, a more rapidly available and completely bioavailable metolazone product. Formulations bioequivalent to Zaroxolyn® and formulations bioequivalent to Mykrox®* should not be interchanged for one another.

* Mykrox® is no longer available in the United States.

VII. Dosing and Administration

The usual dosing regimens for the thiazide-like diuretics are listed in Table 8.

Table 8. 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, 25 mg/day; maintenance, 25 to 100 mg/day	Safety and efficacy in children have not been established.	Tablet: 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 9.

Table 9. 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 to atenolol.	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
				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*	N/A	N/A	$$$
Indapamide	tablet	N/A	N/A	$
Metolazone	tablet	N/A	N/A	$$$

*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 is an alternative treatment option in patients experiencing gynecomastia with spironolactone. Triamterene, metolazone, and hydrochlorothiazide have also been used to treat ascites.[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.[8-10]

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.[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.[8-15] Most patients will require more than one antihypertensive medication to achieve blood pressure goals.[8-14]

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
November 8, 2017

I. Overview

In July 2010, conivaptan and tolvaptan were moved from the miscellaneous diuretics class (AHFS 402892) to a new diuretic subclass, the vasopressin antagonists (AHFS 402828). 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, cirrhosis, 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]

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.[4] 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.[3,4]

The vasopressin antagonists that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. There are no generic products currently available. This class was last reviewed in August 2015.

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	Samsca®	none

^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 patients 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

Clinical Guideline	Recommendation(s)
	abolished, a safe serum sodium level (≥120 mmol/L) is achieved, or a total correction of 18 mmol/L is achieved. ○ 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. ○ 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: ○ 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: ○ The primary therapy of hypothyroidism is thyroid hormone replacement. ○ Hyponatremia with hypothyroidism is infrequent and generally of mild severity; therefore, modest fluid restriction is generally the only treatment necessary. ○ 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): ○ EAH can be severe and life threatening as a result of cerebral edema and noncardiogenic pulmonary edema. ○ Hyponatremia occurring in the setting of endurance exercise is acute, and treatment of symptomatic hyponatremia should be rapid. ○ 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: ○ Hyponatremia from low solute intake is corrected by instituting proper nutrition, with increased content of solute both as electrolytes and protein. • Primary polydipsia: ○ Therapy should be directed at reducing fluid intake into the normal range. ○ 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): ○ 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.

Clinical Guideline	Recommendation(s)
	○ If the serum sodium does not correct to the desired level, lift the fluid restriction and start either conivaptan (if intravenous route is preferred or required) or tolvaptan (if oral therapy is preferred). ○ Hyponatremia in HF is almost always chronic, so current limits for rate of correction of chronic hyponatremias should be observed. ○ 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. ○ 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: ○ There are no guidelines specifically regarding treatment of hyponatremia in cirrhosis. ○ 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: ○ 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. ○ 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

Clinical Guideline	Recommendation(s)
	rates, how important the role of water restriction will remain during chronic use, and whether correction of chronic hyponatremia will result in improved cognitive 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.

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*†
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[5]

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.[1] Tolvaptan is contraindicated in combination with strong cytochrome CYP3A inhibitors, such as

clarithromycin, ketoconazole, itraconazole, ritonavir, indinavir, nelfinavir, saquinavir, nefazodone, and telithromycin.[1] The use of tolvaptan in combination with CYP3A inducers and moderate CYP3A inhibitors should also be avoided.[1]

Table 5. Major Drug Interactions with the Vasopressin Antagonists[5]

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.
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[6]

Adverse Events	Tolvaptan
Cardiovascular	
Ventricular fibrillation	<1
Central Nervous System	
Cerebrovascular accident	<1
Pyrexia	4
Endocrine and Metabolic	
Diabetic ketoacidosis	<1
Hyperglycemia	6
Hypernatremia	<2
Gastrointestinal	
Anorexia	4
Constipation	7
Ischemic colitis	<1
Nausea	21

Adverse Events	Tolvaptan
Xerostomia	7 to 13
Genitourinary	
Pollakiuria	4 to 11
Polyuria	4 to 11
Urethral bleeding	<1
Vaginal hemorrhage	<1
Laboratory Abnormalities	
Bilirubin increased	<1
Prothrombin time prolonged	<1
Musculoskeletal	
Rhabdomyolysis	<1
Weakness	9
Respiratory	
Pulmonary embolism	<1
Respiratory failure	<1
Other	
Deep vein thrombosis	<1
Disseminated intravascular coagulation	<1
Hepatotoxicity	≤4
Hypersensitivity reaction	<1
Skin rash	<1
Thirst	12 to 16

✓ Percent not specified
- Event not reported

Table 7. Boxed Warning for Tolvaptan[2]

WARNING
Tolvaptan 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.

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]

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	Safety and effectiveness have not been established in pediatric patients.	Tablet: 15 mg 30 mg

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.[7] (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.[8] (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.[9] (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)[10] (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.[11] (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.[12] (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.[13] (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.[14] (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.[15] (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.[16] (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.[17] (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.[18] (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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Urine volumes were greater in tolvaptan-treated patients (3,909, 4,232, 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.[19] (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.[20] (2012) Vaptans	MA (12 RCTs) Patients with cirrhosis and	N=2,266 Duration not specified	Primary: Mortality Secondary:	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(tolvaptan, satavaptan*, lixivaptan*) vs control (no intervention, placebo, other diuretics)	hyponatremia or ascites		Complications to cirrhosis (variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis, and hepatorenal syndrome), renal failure, serum sodium levels, mobilization of ascites, safety	Secondary: 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.

*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: 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	Samsca®	$$$$$	N/A

N/A=not available

X. Conclusions

Tolvaptan, the only oral vasopressin antagonist, 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.[2-4]

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.[7,8] 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.[9] Evidence suggests that hyponatremia recurs after discontinuation of tolvaptan.[9,10] Several other studies have evaluated the use of tolvaptan in patients with congestive heart failure as an add-on to conventional treatments.[11-14,16,18,19] 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.[14] 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.[20]

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]

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
November 8, 2017

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 HCV Antivirals
AHFS Class 081840
November 8, 2017

I. Overview

The hepatitis C antivirals are all Food and Drug Administration (FDA)-approved for the treatment of chronic hepatitis C virus (HCV) infection, although differences in indications exist relating to use in specific genotypes. Many patient factors need to be considered when initiating HCV treatment, including but not limited to viral subtype, prior treatment regimen, including response, and presence of cirrhosis. The HCV antivirals also vary with regards to use in combination versus single-product therapy and duration of treatment.[1-11]

HCV is an enveloped ribonucleic acid (RNA) virus that is transmitted through exposure with infected blood. HCV infection is one of the main causes of chronic liver disease worldwide, and the long-term impact of infection is highly variable, from minimal changes to extensive fibrosis and cirrhosis with or without hepatocellular carcinoma.[12] HCV has a highly variable genome and multiple genotypes and subgenotypes, with genotype 1 being the most common in the United States, followed by genotypes 2 and 3.[12] Genotyping is helpful in the clinical management of patients with hepatitis C for determining the choice of therapy. Assessment of liver disease severity is also recommended for predicting prognosis and determining the timing of therapy.[12-14] The goal of hepatitis C treatment is HCV eradication in order to prevent complications and death. Due to the slow evolution of chronic infection, it is difficult to demonstrate if treatment prevents complications of liver disease; therefore, response to treatment is defined by surrogate virological parameters. Sustained virologic response (SVR), defined as the absence of HCV RNA 24 weeks following discontinuation of treatment, has historically been the most important primary endpoint in clinical trials. Recently, SVR 12 (undetectable HCV RNA 12 weeks after the end of therapy) has also been accepted as a primary endpoint for regulatory approval in the United States due to concordance with SVR 24.[12-14]

Over the past 20 years, the success of treatment as evidenced by SVR has steadily increased as new treatments have become available. Treatments with standard interferon resulted in SVR rates of 30 to 60%, depending on genotype. The introduction of peginterferon increased SVR rates to 40 to 70%, and the introduction of direct-acting antivirals has increased SVR to >90%.[12-14] The direct-acting antiviral (DAA) agents act via several different mechanisms of action and include inhibition of non-structural (NS) 3/4A protease, NS5B polymerase, and HCV NS5A.[1-11] Daclatasvir (Daklinza®) binds to the N-terminus of NS5A, a nonstructural protein encoded by HCV, and inhibits both viral ribonucleic acid (RNA) replication and virion assembly.[1] Simeprevir (Olysio®) works via inhibition of the HCV NS3/4A protease of HCV genotype 1a and 1b, thus preventing replication of HCV host cells.[2] Similarly, sofosbuvir (Sovaldi®) inhibits HCV NS5B polymerase which also prevents the replication of HCV host cells; however, it is active against multiple genotypes of HCV.[3]

The combination products that include direct acting HCV antivirals include ledipasvir/sofosbuvir (Harvoni®), ombitasvir/paritaprevir/ritonavir (Technivie®), ombitasvir/paritaprevir/ritonavir/dasabuvir (Viekira®), elbasvir/grazoprevir (Zepatier®) and sofosbuvir/velpatasvir (Epclusa®). Grazoprevir and paritaprevir inhibit NS3/4A protease, dasabuvir inhibits NS5B polymerase and elbasvir, ledipasvir, ombitasvir and velpatasvir specifically inhibit HCV non-structural protein NS5A. Ritonavir, when used in Technivie® and Viekira® products, is used as a boosting agent that increases the peak and trough plasma drug concentrations of paritaprevir along with overall drug exposure; it has no direct effect on the hepatitis C virus.[4-11]

Two new combination products have become available since the last review: Vosevi® (sofosbuvir/velpatasvir/voxilaprevir) was approved in July 2017, and Mavyret® (glecaprevir/pibrentasvir) was approved in August 2017. Vosevi® is a once-daily combination product FDA-approved for the treatment of chronic HCV infection in adults with genotype 1 through 6 without cirrhosis or with compensated cirrhosis. It is the first treatment approved for patients who have been previously treated with a DAA regimen containing sofosbuvir or a NS5A inhibitor. The safety and efficacy has not been established in patients with severe renal impairment, decompensated cirrhosis, or post-liver transplant.[11] Mavyret® is a once-daily combination product FDA-approved for the treatment of chronic HCV infection in adults with genotype 1 through 6 without cirrhosis

or with compensated cirrhosis, including patients with moderate to severe renal impairment or human immunodeficiency virus (HIV)-coinfection. It is also approved for adults with HCV genotype 1 who have been previously treated with an HCV NS5A inhibitor or an NS3/4A protease inhibitor, but not both. It is the first treatment of eight weeks duration approved for all HCV genotypes. Mavyret® is not recommended for patients with decompensated cirrhosis.[7]

Prior to the availability of direct-acting antiviral agents, combination of peginterferon alfa and ribavirin has been the standard of care for the treatment of chronic hepatitis C.[12-14] Guidelines developed by the American Association for the Study of Liver Diseases and Infectious Diseases Society of America in general prefer combination regimens that include newer direct hepatitis C antivirals over older pegylated interferon-based regimens (including those containing older protease inhibitors). The guideline states that although regimens of sofosbuvir and ribavirin or pegylated interferon/ribavirin plus sofosbuvir, simeprevir, telaprevir, or boceprevir are FDA-approved for particular genotypes, they are inferior to the current recommended regimens. The interferon-containing regimens are associated with higher rates of serious adverse events (e.g., anemia and rash), longer treatment duration in some cases, high pill burden, numerous drug-drug interactions, more frequent dosing, and higher intensity of monitoring for safety or treatment response.[13,14]

The HCV antivirals that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. There are no generic products available. This class was last reviewed in February 2017.

Table 1. HCV Antivirals Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Daclatasvir	tablet	Daklinza®	none
Simeprevir	capsule	Olysio®	none
Sofosbuvir	tablet	Sovaldi®	none
Combination Products			
Dasabuvir Sodium, Ombitasvir, Paritaprevir, and Ritonavir	dose pack, extended release tablet	Viekira Pak®, Viekira XR®	Viekira Pak®[CC], Viekira XR®[CC]
Elbasvir and grazoprevir	tablet	Zepatier®	none
Glecaprevir and pibrentasvir	tablet	Mavyret®	none
Ledipasvir and sofosbuvir	tablet	Harvoni®	Harvoni®[CC]
Ombitasvir, paritaprevir, and ritonavir	tablet	Technivie®	Technivie®[CC]
Sofosbuvir and velpatasvir	tablet	Epclusa®	none
Sofosbuvir, velpatasvir, and voxilaprevir	tablet	Vosevi®	none

PDL=Preferred Drug List
[CC]Denotes agent is preferred with clinical criteria in place.

II. Evidence-Based Medicine and Current Treatment Guidelines

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

Table 2. Treatment Guidelines Using the HCV Antivirals

Clinical Guideline	Recommendation(s)
American Association for the Study of Liver Diseases and Infectious Diseases Society of America: **Recommendations for testing,**	Goal of treatment • The goal of treatment of hepatitis C virus (HCV)-infected persons is to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of virologic cure as evidenced by a sustained virologic response (SVR). When and in whom to initiate treatment • Treatment is recommended for all patients with chronic HCV infection, except

Clinical Guideline	Recommendation(s)

managing, and treating hepatitis C (2017)[13]	those with short life expectancies that cannot be remediated by treating HCV, by transplantation, or by other directed therapy. Patients with short life expectancies owing to liver disease should be managed in consultation with an expert.
	• An evaluation of advanced fibrosis using liver biopsy, imaging, and/or noninvasive markers is recommended.
	• There are no data to support pretreatment screening for illicit drug or alcohol use in identifying a population more likely to successfully complete HCV therapy. These requirements should be abandoned, because they create barriers to treatment, add unnecessary cost and effort, and potentially exclude populations that are likely to obtain substantial benefit from therapy.
	• Strong and accumulating evidence argue against deferral because of decreased all-cause morbidity and mortality, prevention of onward transmission, and quality-of-life improvements for patients treated regardless of baseline fibrosis. Deferral practices based on fibrosis stage alone are inadequate and shortsighted. Ongoing assessment of liver disease is recommended for persons in whom therapy is deferred.
	• Recommended and alternative regimens below are generally listed in groups by level of evidence, then alphabetically.
	
	<u>Initial treatment of HCV infection (treatment-naïve)</u>
	• <u>Genotype 1a (no cirrhosis)</u>
	  ○ Elbasvir/grazoprevir for 12 weeks (baseline NS5A resistance-associated substitutions [RAS] absent)
	  ○ Ledipasvir/sofosbuvir for 12 weeks
	  ○ Ledipasvir/sofosbuvir for eight weeks (non-black, HCV-monoinfected, HCV RNA <6 million IU/mL)
	  ○ Paritaprevir/ritonavir/ombitasvir plus dasabuvir and ribavirin for 12 weeks
	  ○ Sofosbuvir plus simeprevir for 12 weeks
	  ○ Sofosbuvir/velpatasvir for 12 weeks
	  ○ Daclatasvir plus sofosbuvir for 12 weeks
	  ○ Alternative: elbasvir/grazoprevir and ribavirin 16 weeks (baseline NS5A RAS present)
	• <u>Genotype 1a (compensated cirrhosis)</u>
	  ○ Elbasvir/grazoprevir for 12 weeks (baseline NS5A RAS absent)
	  ○ Ledipasvir/sofosbuvir for 12 weeks
	  ○ Sofosbuvir/velpatasvir for 12 weeks
	  ○ Alternative: paritaprevir/ritonavir/ombitasvir plus dasabuvir and ribavirin for 24 weeks
	  ○ Alternative: sofosbuvir plus simeprevir with or without ribavirin for 24 weeks (Q80K polymorphism not detected)
	  ○ Alternative: daclatasvir plus sofosbuvir with or without ribavirin for 24 weeks.
	  ○ Alternative: elbasvir/grazoprevir and ribavirin 16 weeks (baseline NS5A RAS present)
	• <u>Genotype 1b (no cirrhosis)</u>
	  ○ Elbasvir/grazoprevir for 12 weeks
	  ○ Ledipasvir/sofosbuvir for 12 weeks
	  ○ Ledipasvir/sofosbuvir for eight weeks (non-black, HCV-monoinfected, HCV RNA <6 million IU/mL)
	  ○ Paritaprevir/ritonavir/ombitasvir plus dasabuvir for 12 weeks
	  ○ Sofosbuvir plus simeprevir for 12 weeks
	  ○ Sofosbuvir/velpatasvir for 12 weeks
	  ○ Daclatasvir plus sofosbuvir for 12 weeks
	• <u>Genotype 1b (compensated cirrhosis)</u>
	  ○ Elbasvir/grazoprevir for 12 weeks
	  ○ Ledipasvir/sofosbuvir for 12 weeks

Clinical Guideline	Recommendation(s)
	○ Paritaprevir/ritonavir/ombitasvir plus dasabuvir for 12 weeks ○ Alternative: sofosbuvir plus simeprevir with or without ribavirin for 24 weeks ○ Alternative: daclatasvir plus sofosbuvir with or without ribavirin for 24 weeks. • Shortening treatment with ledipasvir/sofosbuvir to less than 12 weeks for patients without cirrhosis should be done at the discretion of the practitioner with consideration for potential negative prognostic factors. • Genotype 2 ○ Sofosbuvir/velpatasvir for 12 weeks ○ Alternative: Daclatasvir plus sofosbuvir for 12 weeks (no cirrhosis) or 16 to 24 weeks (compensated cirrhosis) • Genotype 3 ○ Sofosbuvir/velpatasvir for 12 weeks ○ Daclatasvir plus sofosbuvir for 12 weeks (no cirrhosis) or with or without ribavirin for 24 weeks (compensated cirrhosis) ○ Testing for Y93H polymorphism is recommended for cirrhotic patients and ribavirin should be included in regimen if present. • Genotype 4 ○ Paritaprevir/ritonavir/ombitasvir and ribavirin for 12 weeks ○ Sofosbuvir/velpatasvir for 12 weeks ○ Elbasvir/grazoprevir for 12 weeks ○ Ledipasvir/sofosbuvir for 12 weeks • Genotype 5 or 6 ○ Sofosbuvir/velpatasvir for 12 weeks ○ Ledipasvir/sofosbuvir for 12 weeks Retreatment after failed therapy (peginterferon alfa and ribavirin) • Genotype 1a (no cirrhosis) ○ Elbasvir/grazoprevir for 12 weeks (baseline NS5A RAS absent) ○ Ledipasvir/sofosbuvir for 12 weeks ○ Paritaprevir/ritonavir/ombitasvir plus dasabuvir and ribavirin for 12 weeks ○ Sofosbuvir plus simeprevir for 12 weeks ○ Sofosbuvir/velpatasvir for 12 weeks ○ Daclatasvir plus sofosbuvir for 12 weeks ○ Alternative: elbasvir/grazoprevir and ribavirin 16 weeks (baseline NS5A RAS present) • Genotype 1a (compensated cirrhosis) ○ Elbasvir/grazoprevir for 12 weeks (baseline NS5A RAS absent) ○ Ledipasvir/sofosbuvir and ribavirin for 12 weeks ○ Sofosbuvir/velpatasvir for 12 weeks ○ Alternative: paritaprevir/ritonavir/ombitasvir plus dasabuvir and ribavirin for 24 weeks ○ Alternative: ledipasvir/sofosbuvir for 24 weeks ○ Alternative: elbasvir/grazoprevir and ribavirin 16 weeks (baseline NS5A RAS present) ○ Alternative: daclatasvir plus sofosbuvir with or without ribavirin for 24 weeks. ○ Alternative: sofosbuvir plus simeprevir with or without ribavirin for 24 weeks (Q80K polymorphism not detected) • Genotype 1b (no cirrhosis) ○ Elbasvir/grazoprevir for 12 weeks ○ Ledipasvir/sofosbuvir for 12 weeks ○ Paritaprevir/ritonavir/ombitasvir plus dasabuvir for 12 weeks ○ Sofosbuvir plus simeprevir for 12 weeks ○ Sofosbuvir/velpatasvir for 12 weeks

Clinical Guideline	Recommendation(s)
	○ Daclatasvir plus sofosbuvir for 12 weeks • Genotype 1b (compensated cirrhosis) ○ Elbasvir/grazoprevir for 12 weeks ○ Ledipasvir/sofosbuvir and ribavirin for 12 weeks ○ Paritaprevir/ritonavir/ombitasvir plus dasabuvir for 12 weeks ○ Sofosbuvir/velpatasvir for 12 weeks ○ Alternative: ledipasvir/sofosbuvir for 24 weeks ○ Alternative: sofosbuvir plus simeprevir with or without ribavirin for 24 weeks ○ Alternative: daclatasvir plus sofosbuvir with or without ribavirin for 24 weeks • Genotype 2 ○ Sofosbuvir/velpatasvir for 12 weeks ○ Alternative: Daclatasvir plus sofosbuvir for 12 weeks (no cirrhosis) or 16 to 24 weeks (compensated cirrhosis) • Genotype 3 ○ Sofosbuvir/velpatasvir for 12 weeks (no cirrhosis) or 12 weeks with ribavirin (compensated cirrhosis) ○ Daclatasvir plus sofosbuvir for 12 weeks (no cirrhosis) ○ Elbasvir/grazoprevir plus sofosbuvir for 12 weeks (compensated cirrhosis) ○ Alternative: daclatasvir plus sofosbuvir and ribavirin for 24 weeks (compensated cirrhosis) ○ Testing for Y93H polymorphism is recommended for patients without cirrhosis and ribavirin should be included in regimen if present. • Genotype 4 ○ Paritaprevir/ritonavir/ombitasvir and ribavirin for 12 weeks ○ Sofosbuvir/velpatasvir for 12 weeks ○ Elbasvir/grazoprevir for 12 weeks (virologic relapse after prior peginterferon alfa and ribavirin) or 16 weeks with ribavirin (failure to suppress or breakthrough on prior peginterferon alfa and ribavirin) ○ Ledipasvir/sofosbuvir for 12 weeks (no cirrhosis) or 12 weeks with ribavirin (compensated cirrhosis) ○ Alternative: Ledipasvir/sofosbuvir for 24 weeks (compensated cirrhosis) • Genotype 5 or 6 ○ Ledipasvir/sofosbuvir for 12 weeks ○ Sofosbuvir/velpatasvir for 12 weeks • Mixed Genotypes ○ Treatment data for mixed genotypes with direct-acting antivirals (DAA) are sparse but utilization of a pangenotypic regimen should be considered. Retreatment after failed therapy (sofosbuvir and ribavirin with or without peginterferon alfa) • Genotype 1 ○ Ledipasvir/sofosbuvir and ribavirin for 12 weeks (no cirrhosis) or 24 weeks (compensated cirrhosis) Retreatment after failed therapy (HCV protease inhibitor plus peginterferon alfa and ribavirin) • Genotype 1 (no cirrhosis) ○ Ledipasvir/sofosbuvir for 12 weeks ○ Sofosbuvir/velpatasvir for 12 weeks ○ Daclatasvir plus sofosbuvir for 12 weeks ○ Elbasvir/grazoprevir and ribavirin for 12 weeks (baseline NS5A RAS absent) or 16 weeks (for genotype 1a with baseline NS5A RAS present) • Genotype 1 (compensated cirrhosis) ○ Ledipasvir/sofosbuvir and ribavirin for 12 weeks

Clinical Guideline	Recommendation(s)
	○ Ledipasvir/sofosbuvir for 24 weeks ○ Daclatasvir plus sofosbuvir with or without ribavirin for 24 weeks ○ Elbasvir/grazoprevir and ribavirin for 12 weeks (baseline NS5A RAS absent) or 16 weeks (for genotype 1a with baseline NS5A RAS present) Retreatment after failed therapy (sofosbuvir plus simeprevir or HCV NS5A inhibitor) • Genotype 1 ○ Deferral of treatment is recommended for patients who do not have cirrhosis and do not have reasons for urgent treatment ○ Testing for RAS that confer decreased susceptibility to NS3 protease inhibitors and to NS5A inhibitors is recommended who have compensated cirrhosis or have reasons for urgent retreatment. Specific drugs should be tailored to the results of this testing. ○ When using nucleotide-based (e.g., sofosbuvir) dual DAA therapy treatment duration of 24 weeks is recommended, with ribavirin, unless contraindicated. ○ If available, nucleotide-based (e.g., sofosbuvir) triple or quadruple DAA regimens may be considered for 12 to 24 weeks with ribavirin, unless contraindicated. Retreatment after failed therapy (sofosbuvir and ribavirin) • Genotype 2 ○ Daclatasvir plus sofosbuvir with or without ribavirin for 24 weeks ○ Sofosbuvir/velpatasvir plus ribavirin for 12 weeks • Genotype 3 ○ Deferral of treatment is recommended for patients who do not have cirrhosis and do not have reasons for urgent treatment ○ Daclatasvir plus sofosbuvir and ribavirin for 24 weeks ○ Elbasvir/grazoprevir plus sofosbuvir with or without ribavirin for 12 to 16 weeks ○ Sofosbuvir/velpatasvir plus ribavirin for 12 weeks Recommendations for discontinuation of treatment due to lack of efficacy • If HCV viral load is detectable at week four, repeat quantitative HCV viral load after two additional weeks of treatment (treatment week six). ○ If quantitative HCV viral load has increased by greater than 10-fold (>1 $\log_{10}$ IU/mL) on repeat testing at week six (or thereafter), discontinue HCV treatment. • The significance of a positive HCV RNA test result at week 4 that remains positive, but lower, at week six or week eight is unknown. ○ No recommendation to stop therapy or extend therapy can be provided at this time. Special populations – human immunodeficiency virus (HIV)/HCV coinfection • HIV/HCV-coinfected persons should be treated and re-treated the same as persons without HIV infection, after recognizing and managing interactions with antiretroviral medications. • Daclatasvir and sofosbuvir, with or without ribavirin is recommended when antiretroviral regimen changes cannot be made to accommodate alternative HCV DAA Special populations – decompensated cirrhosis • Patients with decompensated cirrhosis (Child Turcotte Pugh [CTP] class B or C) should be referred to a medical practitioner with expertise in that condition (ideally in a liver transplant center). • Genotype 1, 4, 5, or 6 (patients who may or may not be candidates for liver

Clinical Guideline	Recommendation(s)
	transplantation, including those with hepatocellular carcinoma) ○ Ledipasvir/sofosbuvir and ribavirin for 12 weeks ○ Sofosbuvir/velpatasvir plus ribavirin for 12 weeks ○ Daclatasvir plus sofosbuvir and ribavirin for 12 weeks (genotype 1 or 4 only) ○ Alternative (ribavirin ineligible): sofosbuvir/velpatasvir for 24 weeks ○ Alternative (ribavirin ineligible): daclatasvir plus sofosbuvir for 24 weeks (genotype 1 or 4 only) ○ Alternative (ribavirin ineligible): ledipasvir/sofosbuvir for 24 weeks ○ Alternative (prior failure with a sofosbuvir-based or NS5A-based regimen): ledipasvir/sofosbuvir or sofosbuvir/velpatasvir 24 weeks with ribavirin • Genotype 2 or 3 (patients who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma) ○ Sofosbuvir/velpatasvir plus ribavirin for 12 weeks ○ Daclatasvir plus sofosbuvir and ribavirin for 12 weeks Special populations – recurrent HCV infection post-liver transplantation • Genotype 1 or 4 infection in the allograft (including compensated cirrhosis), treatment-naïve or treatment-experienced ○ Ledipasvir/sofosbuvir with ribavirin for 12 weeks (including decompensated cirrhosis) ○ Daclatasvir plus sofosbuvir and ribavirin for 12 weeks ○ Alternative (ribavirin ineligible): ledipasvir/sofosbuvir for 24 weeks (treatment-naïve only) ○ Alternative (ribavirin ineligible): daclatasvir plus sofosbuvir for 24 weeks (treatment-naïve only) ○ Alternative (genotype 1 only): sofosbuvir plus simeprevir with or without ribavirin for 12 weeks ○ Alternative (genotype 1, Metavir fibrosis stage F0-F2): paritaprevir/ritonavir/ombitasvir plus dasabuvir and ribavirin for 24 weeks • Genotype 2 infection in the allograft (including compensated cirrhosis), treatment-naïve or treatment-experienced ○ Daclatasvir plus sofosbuvir and ribavirin for 12 weeks ○ Sofosbuvir and ribavirin for 24 weeks ○ Alternative (ribavirin ineligible): daclatasvir plus sofosbuvir for 24 weeks • Genotype 2 infection in the allograft, liver transplant recipients (with decompensated cirrhosis), treatment-naïve or treatment-experienced ○ Sofosbuvir and ribavirin for 24 weeks • Genotype 3 infection in the allograft (including compensated cirrhosis), treatment-naïve or treatment-experienced ○ Daclatasvir plus sofosbuvir and ribavirin for 12 weeks ○ Alternative (ribavirin ineligible): daclatasvir plus sofosbuvir for 24 weeks Special populations – renal impairment • Mild to moderate renal impairment (CrCl ≥30 mL/min) ○ Daclatasvir: no dosage adjustment is required ○ Ledipasvir/sofosbuvir: no dosage adjustment is required ○ Paritaprevir/ritonavir/ombitasvir with and without dasabuvir: no dosage adjustment is required ○ Simeprevir: no dosage adjustment is required ○ Sofosbuvir: no dosage adjustment is required • Severe renal impairment (CrCl<30 mL/min or end-stage renal disease) with high urgency to treat and kidney transplant is not an immediate option ○ HCV genotype 1a, 1b or 4 infection: elbasvir/grazoprevir for 12 weeks ○ HCV genotype 1b infection: paritaprevir/ritonavir/ombitasvir plus dasabuvir ○ HCV genotype 2, 3, 5, or 6 infection: peginterferon alfa and ribavirin

Clinical Guideline	Recommendation(s)
	○ Alternative (HCV genotype 1a infection): daily paritaprevir/ritonavir/ombitasvir plus dasabuvir (and ribavirin if hemoglobin >10 g/dL at a dose of 200 mg daily) Management of acute HCV infection • HCV antibody and HCV RNA testing are recommended when acute HCV infection is suspected due to exposure, clinical presentation, or elevated aminotransferase levels • Preexposure or postexposure prophylaxis with antiviral therapy is NOT recommended. • Medical management and monitoring ○ Regular laboratory monitoring is recommended in the setting of acute HCV infection. Monitoring HCV RNA (every four to eight weeks) for six to 12 months is recommended to determine spontaneous clearance of HCV infection versus persistence of infection. ○ Counseling is recommended for patients with acute HCV infection to avoid hepatotoxic insults including hepatotoxic drugs and alcohol consumption, and to reduce the risk of HCV transmission to others. ○ Referral to an addiction medicine specialist is recommended for patients with acute HCV infection related to substance use. • Treatment for patients with acute HCV infection ○ If treatment is delayed, monitoring for spontaneous clearance is recommended for a minimum of six months. ○ If treatment is to begin during the acute infection period, monitor HCV RNA for at least 12 to 16 weeks before starting treatment to allow for spontaneous clearance. ○ Treatment with the same standard regimens is recommended for chronic and acute HCV infection
Department of Veterans Affairs National Hepatitis C Resource Center Program and the Office of Public Health: **HCV Infection: Treatment Considerations (2017)**[14]	Goal of treatment • The goal of hepatitis C antiviral treatment is to achieve a SVR, defined as undetectable HCV RNA in the blood 12 or more weeks after completing antiviral treatment. Principles for patient selection for HCV treatment • All patients with chronic HCV who do not have medical contraindications are potential candidates for antiviral treatment. • The urgency of treating HCV should be based on the risk of developing decompensated cirrhosis or dying from liver or liver-related disease, and prolonging graft survival in liver transplant recipients. • Urgent treatment should be considered in patients with advanced cirrhosis, selected patients with hepatocellular carcinoma (HCC) awaiting liver transplant, post-transplant recipients with cirrhosis, and patients with serious extra-hepatic manifestations of HCV, and women of childbearing potential who desire to conceive a child in the next 12 months. • Patients with mild liver disease (METAVIR F0 to F2) have less urgency for treatment in the short term, but should be informed of current treatments and their potential to cure HCV. • Patients with severe mental health conditions who are engaged in treatment or those with ongoing substance use including drinking alcohol, using illicit drugs, including marijuana, or participating in opioid replacement programs should not be excluded from HCV treatment. • Treatment is not indicated in patients with limited life expectancy of less than 12 months unless there is reason to anticipate that duration or quality of life can be improved by eradication of HCV. • Factors that may complicate adherence, such as active substance abuse,

Clinical Guideline	Recommendation(s)

	depression, neurocognitive disorders, and lack of social support, should be addressed before initiating medications.
	
	Treatment of HCV genotype 1 in treatment-naïve patients without cirrhosis
	• Ledipasvir/sofosbuvir for eight weeks if baseline HCV RNA <6 million IU/mL; 12 weeks if HIV/HCV co-infected or HCV RNA ≥6 million IU/mL (alternative in African Americans and those with detectable HCV RNA at treatment week 4).
	
	Treatment of HCV genotype 1 in treatment-naïve or -experienced (prior peginterferon alfa and ribavirin) patients without or with cirrhosis (CTP A)
	• Elbasvir/grazoprevir
	  ○ Genotype 1a without baseline NS5A RAS: 12 weeks.
	  ○ Genotype 1a with baseline NS5A RAS: 16 weeks with ribavirin.
	  ○ Genotype 1b: 12 weeks.
	• Ledipasvir/sofosbuvir for 12 weeks (with ribavirin if treatment-experienced with cirrhosis).
	• Paritaprevir/ritonavir/ombitasvir/dasabuvir
	  ○ Genotype 1a: 12 weeks with ribavirin
	  ○ Genotype 1b: 12 weeks with or without ribavirin
	  ○ May consider 24 weeks in cirrhotics or prior null responders
	
	Treatment of HCV genotype 1 in treatment-experienced (prior NS3/4A inhibitor plus peginterferon alfa and ribavirin, or prior sofosbuvir and ribavirin with or without peginterferon alfa) patients without or with cirrhosis (CTP A)
	• Elbasvir/grazoprevir and ribavirin
	  ○ Genotype 1a without baseline NS5A RAS: 12 weeks.
	  ○ Genotype 1a with baseline NS5A RAS: 16 weeks.
	  ○ Genotype 1b: 12 weeks.
	• Ledipasvir/sofosbuvir and ribavirin for 12 weeks
	
	Treatment of HCV genotype 1 in treatment-naïve or -experienced (prior peginterferon alfa and ribavirin, prior NS3/4A inhibitor plus peginterferon alfa and ribavirin, or prior sofosbuvir and ribavirin with or without peginterferon alfa) patients with decompensated cirrhosis (CTP B or C)
	• Ledipasvir/sofosbuvir and ribavirin for 12 weeks
	
	Treatment of HCV genotype 1 in treatment-experienced (prior NS5A-containing regimen) patients with or without cirrhosis
	• Test for RAS to NS5A prior to re-treatment and consult with an expert.
	
	Treatment of HCV genotype 2 in treatment-naïve patients with or without cirrhosis (CTP A)
	• Sofosbuvir/velpatasvir for 12 weeks (with ribavirin if sofosbuvir-experienced)
	
	Treatment of HCV genotype 2 in treatment-naïve or treatment-experienced patients with decompensated cirrhosis (CTP B or C)
	• Sofosbuvir/velpatasvir plus ribavirin for 12 weeks
	
	Treatment of HCV genotype 3 in treatment-naïve patients without cirrhosis
	• Sofosbuvir/velpatasvir for 12 weeks
	
	Treatment of HCV genotype 3 in treatment-naïve patients with cirrhosis (CTP A) or treatment-experienced patients (prior sofosbuvir and ribavirin with or without peginterferon alfa) with or without cirrhosis (CTP A)
	• Sofosbuvir/velpatasvir for 12 weeks (with ribavirin if sofosbuvir-experienced or

Clinical Guideline	Recommendation(s)

	NS5A Y93H RAS is present)
	
	Treatment of HCV genotype 3 in treatment-naïve or treatment-experienced (prior sofosbuvir and ribavirin with or without peginterferon alfa) patients with decompensated cirrhosis (CTP B or C)
	• Sofosbuvir/velpatasvir and ribavirin for 12 weeks
	
	Treatment of HCV genotype 4 in treatment-naïve and treatment-experienced patients (peginterferon alfa and ribavirin only) patients with or without cirrhosis (CTP A)
	• Elbasvir/grazoprevir for 12 weeks (with ribavirin for 16 weeks if treatment-experienced)
	• Ledipasvir/sofosbuvir for 12 weeks
	• Paritaprevir/ritonavir/ombitasvir and ribavirin for 12 weeks.
	
	Treatment of HCV genotype 4 in treatment-naïve and treatment-experienced patients (peginterferon alfa and ribavirin only) patients with decompensated cirrhosis (CTP B or C)
	• Ledipasvir/sofosbuvir and ribavirin for 12 weeks
	• Alternative: sofosbuvir/velpatasvir and ribavirin for 12 weeks
	
	Stopping rules based on lack of virologic response
	• Patients should have an HCV RNA level assessed at week 4 of treatment.
	• If the HCV RNA is quantifiable at week 4 or at any time point thereafter, reassess HCV RNA in two weeks. If the repeated HCV RNA increases (i.e., >1 $\log_{10}$ IU/mL from nadir), discontinuation of all treatment should be strongly considered.
	• HCV RNA levels should be assessed at 12 weeks after completion of treatment to determine whether SVR was achieved.
	
	Use in HIV/HCV-coinfection
	• HIV/HCV-coinfected patients receive the same HCV antiviral regimen as HCV-monoinfected patients (except for eight weeks with ledipasvir/sofosbuvir), provided the patient is receiving appropriate HIV care and drug-drug interactions are addressed appropriately.
	
	Treatment in pre- or post-liver transplant
	• Genotype 1 or 4, including patients with CTP A, B, or C, or HCC
	  ○ Ledipasvir/sofosbuvir and ribavirin for 12 weeks
	• Genotype 2, including patients with HCC
	  ○ Sofosbuvir/velpatasvir for 12 weeks (with ribavirin if sofosbuvir-experienced, or CTP B or C)
	• Genotype 3, including patients with HCC
	  ○ Sofosbuvir/velpatasvir for 12 weeks (with ribavirin if sofosbuvir-experienced, if NS5A Y93H is present, or if CTP B or C)

III. Indications

The Food and Drug Administration (FDA)-approved indications for the HCV antivirals 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 Single-Entity HCV Antivirals[1-11]

Indication	Daclatasvir	Simeprevir	Sofosbuvir
Hepatitis C			
Treatment of chronic HCV genotype 1 infection	✔ *	✔ *	✔ *
Treatment of chronic HCV genotype 2 infection			✔ *
Treatment of chronic HCV genotype 3 infection	✔ *		✔ *
Treatment of chronic HCV genotype 4 infection		✔ *	✔ *

*as a component of a combination antiviral treatment regimen.
HCV=Hepatitis C Virus

Table 4. FDA-Approved Indications for the Combination Product HCV Antivirals[1-11]

Indication	Dasabuvir/ ombitasvir/ pritaprevir/ ritonavir	Elbasvir/ grazoprevir	Glecaprevir/ pibrentasvir	Ledipasvir/ sofosbuvir	Ombitasvir/ aritaprevir/ ritonavir	Sofosbuvir/velpatasvir	Sofosbuvir/ velpatasvir/ voxilaprevev
Hepatitis C							
Treatment of chronic HCV genotype 1 infection	✔ †	✔ †	✔	✔ †		✔ †	✔ ‡
Treatment of chronic HCV genotype 2 infection			✔			✔ †	✔ ‡
Treatment of chronic HCV genotype 3 infection			✔			✔ †	✔ ‡
Treatment of chronic HCV genotype 4 infection		✔ †	✔	✔ †	✔ *	✔ †	✔ ‡
Treatment of chronic HCV genotype 5 infection			✔	✔		✔ †	✔ ‡
Treatment of chronic HCV genotype 6 infection			✔	✔		✔ †	✔ ‡

*as a component of a combination antiviral treatment regimen.
†with or without ribavirin.
‡in patients who have genotype 1, 2, 3, 4, 5, or 6 infection and have previously been treated with an HCV regimen containing an NS5A inhibitor; and in patients who have genotype 1a or 3 infection and have previously been treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor.
HCV=Hepatitis C Virus

IV. Pharmacokinetics

The pharmacokinetic parameters of the HCV antivirals are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the HCV Antivirals[15]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Daclatasvir	67	99	Liver	Renal (7) Feces (88)	12 to 15
Simeprevir	62	>99	Liver	Renal (<1) Feces (91)	41
Sofosbuvir	Not reported	61 to 65	Liver	Renal (80) Feces (14)	0.4
Combination Products					
Dasabuvir, ombitasvir, paritaprevir, and ritonavir	OPR: Not reported D: 70	O: >99 P: 97 to 99 R: >99 D: >99	O: Various locations P: Liver R: Liver D: Liver	O: Renal (2) Feces (90); P: Renal (9) Feces (88); R: Renal (11) Feces (86); D: Renal (2) Feces (94)	O: 21 to 25 P: 5.5 R: 4 D: 5.5 to 6
Elbasvir and grazoprevir	Not reported	E: >99 G: >98	Liver	Renal (<1) Feces (>90)	E: 24 G: 31

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Glecaprevir and pibrentasvir	Not reported	Gl: >97 Pi: >99	Gl: Liver Pi: Liver	Gl: Renal (<1) Feces (>92) Pi: Feces (>96)	Gl: 6 to 9.8 Pi: 13 to 27.4
Ledipasvir and sofosbuvir	Not reported	L: >99 S: 61 to 65	L: Unknown S: Liver	L: Feces (86) S: Renal (80) Feces (14)	L: 47 S: 0.5
Ombitasvir, paritaprevir, and ritonavir	Well absorbed	O: >99 P: 97 to 99 R: >99	O: Various locations P: Liver R: Liver	O: Renal (2) Feces (90); P: Renal (9) Feces (88); R: Renal (11) Feces (86)	O: 21 to 25 P: 5.5 R: 4
Sofosbuvir and velpatasvir	Not reported	S: 61 to 65 V: >99	Liver	S: Renal (80) Feces (14) V: Renal (0.4) Feces (94)	S: 0.5 V: 17
Sofosbuvir, velpatasvir, and voxilaprevir	Not reported	S: 61 to 65 V: >99 Vox: >99	Liver	S: Renal (80) Feces (14) V: Renal (0.4) Feces (94) Vox: Feces (94)	S: 0.5 V: 17 Vox: 33

L=ledipasvir, S=sofosbuvir, O=ombitasvir, P=paritaprevir, R=ritonavir, D=dasabuvir, E=elbasvir, G=grazoprevir, Gl=glecaprevir, Pi=pibrentasvir, V=velpatasvir, Vox=voxilaprevir.

V. Drug Interactions

Major drug interactions with the HCV antivirals are listed in Tables 6 through 15.[1-11]

Table 6. Drug Interactions with simeprevir-containing regimens (Not All Inclusive)

Concomitant HIV-antivirals: Coadministration with any the following HIV antiretrovirals is not recommended based on Olysio® prescribing information and the AASLD/IDSA guidelines	
Aptivus® (tipranavir)	Norvir® (ritonavir)
Atripla® (efavirenz/emtricitabine/tenofovir disoproxil fumarate)	Prezista® (darunavir)/ritonavir
Crixivan® (indinavir)	Rescriptor® (delavirdine)
Genvoya® (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide)	Reyataz® (atazanavir)/ritonavir
Intelence® (etravirine)	Sustiva® (efavirenz)
Invirase® (saquinavir)	Stribild® (elvitegravir/cobicistat/emtricitabine/tenofovir) or
Kaletra® (lopinavir/ritonavir)	Viramune® (nevirapine)
Lexiva (fosamprenavir)/ritonavir	Viracept® (nelfinavir)

Table 7. Drug Interactions with daclatasvir plus sofosbuvir regimens (Not All Inclusive)

Concomitant Drug Class: Drug Name	Effect on Concentration	Recommendations
Anticonvulsants:		
Anticonvulsants: carbamazepine, phenytoin, phenobarbital,	↓ sofosbuvir ↓ GS-331007 (metabolite)	Coadministration of Sovaldi® with carbamazepine, phenytoin, phenobarbital, or oxcarbazepine may decrease sofosbuvir concentration, leading to reduced therapeutic. Coadministration is not recommended.

Concomitant Drug Class: Drug Name	Effect on Concentration	Recommendations
oxcarbazepine		
Antimycobacterial:		
rifabutin, rifampin, rifapentine	↓ sofosbuvir ↓ GS-331007 (metabolite)	Coadministration of Sovaldi® with rifabutin or rifapentine may decrease sofosbuvir concentration, leading to reduced therapeutic effect of Sovaldi®. Coadministration is not recommended. Coadministration with rifampin, a P-gp inducer, is not recommended.
Strong CYP3A inhibitors		
Examples: atazanavir/ritonavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, saquinavir, telithromycin, and voriconazole	↑ daclatasvir	Decrease Daklinza® (daclatasvir) dose to 30 mg once daily when coadministering with strong inhibitors of CYP3A.
Moderate CYP3A inducers		
Examples: bosentan, dexamethasone, **efavirenz**, **etravirine,** modafinil, nafcillin, rifapentine	↓ daclatasvir	Increase Daklinza® (daclatasvir) dose to 90 mg once daily when coadministering with moderate inducers of CYP3A **– *Since 90 mg strength is available, requests to combine 30 mg and 60 mg strengths to achieve 90 mg total daily dose should be denied***
Anticoagulants		
Dabigatran etexilate mesylate	↑ dabigatran	In patients being treated with dabigatran for recurrent deep vein thrombosis and pulmonary embolism, avoid Daklinza® if CrCl<50 mL/min. Co-administration is not recommended in severe renal impairment (CrCl 15 to 30 mL/min) for all other patients.
Cardiovascular agents		
Antiarrhythmics: Amiodarone with another direct-acting antiviral (e.g., Sovaldi®)	unknown	Coadministration Daklinza® with another direct-acting antiviral (e.g., Sovaldi®) **and** amiodarone may result in serious symptomatic bradycardia and is not recommended. If coadministration is required, inpatient cardiac monitoring is recommended.
Antiarrhythmic: Digoxin	↑ digoxin	*Patients on daclatasvir initiating digoxin:* Use the lowest dosage of digoxin, monitor digoxin concentrations, and adjust digoxin doses, if necessary. *Patients on digoxin prior to initiating daclatasvir:* Measure digoxin concentrations before initiating daclatasvir, decrease digoxin dosage by approximately 30 to 50% or by modifying the dosing frequency and continue monitoring.
Herbal Supplements: St. John's wort	↓ sofosbuvir ↓ GS-331007 (metabolite)	Coadministration of Sovaldi® with St. John's wort, a P-gp inducer is not recommended.
Aptivus® (tipranavir)/ritonavir	↓ sofosbuvir ↓ GS-331007 (metabolite)	Coadministration of Sovaldi® with tipranavir/ritonavir may decrease sofosbuvir concentration, leading to reduced therapeutic effect of Sovaldi®. Coadministration is not recommended.

Table 8. Drug Interactions with sofosbuvir (Not All Inclusive)

Concomitant Drug Class: Drug Name	Effect on Concentration	Recommendations
Antiarrhythmics: Amiodarone with another direct-acting antiviral (e.g., Daklinza®, Olysio®)	unknown	Coadministration of Sovaldi® with another direct-acting antiviral (e.g., Daklinza® or Olysio®) **and** amiodarone may result in serious symptomatic bradycardia and is not recommended. If coadministration is required, inpatient cardiac monitoring is recommended.
Anticonvulsants: carbamazepine, phenytoin, phenobarbital, oxcarbazepine	↓ sofosbuvir ↓ GS-331007 (metabolite)	Coadministration with carbamazepine, phenytoin, phenobarbital, or oxcarbazepine may decrease sofosbuvir concentration, leading to reduced therapeutic effect of Sovaldi®. Coadministration is not recommended.
Antimycobacterial: rifabutin, rifampin, rifapentine	↓ sofosbuvir ↓ GS-331007 (metabolite)	Coadministration with rifabutin or rifapentine may decrease sofosbuvir concentration, leading to reduced therapeutic effect of Sovaldi®. Coadministration is not recommended. Coadministration with rifampin, a P-gp inducer, is not recommended.
Herbal Supplements: St. John's wort	↓ sofosbuvir ↓ GS-331007 (metabolite)	Coadministration of Sovaldi® with St. John's wort, a P-gp inducer is not recommended.
Aptivus® (tipranavir)/ritonavir	↓ sofosbuvir ↓ GS-331007 (metabolite)	Coadministration with tipranavir/ritonavir may decrease sofosbuvir concentration, leading to reduced therapeutic effect of Sovaldi®. Coadministration is not recommended.

Table 9. Drug Interactions with ledipasvir/sofosbuvir (Not All Inclusive)

Concomitant Drug Class: Drug Name	Effect on Concentration	Recommendations
H_2-receptor antagonists: famotidine	↓ ledipasvir	H_2-receptor antagonist doses greater than famotidine 40 mg twice daily (or equivalent H_2-receptor antagonist) may decrease ledipasvir concentration. **H_2 antagonist** — **Comparable dose** Tagamet® (cimetidine) — 400 mg to 800 mg twice daily Pepcid® (famotidine) — 40 mg twice daily Axid® (nizatidine) — 300 mg twice daily Zantac® (ranitidine) — 150 mg four times daily
Proton-pump inhibitors (PPI): such as omeprazole	↓ ledipasvir	PPI doses greater than omeprazole 20 mg daily (or equivalent PPI) may decrease ledipasvir concentration. **Proton-pump inhibitor** — **Comparable dose** Aciphex® (rabeprazole) — 20 mg Dexilant® (dexlansoprazole) — 30 mg Nexium® (esomeprazole) — 20 mg Prevacid® (lansoprazole) — 30 mg Prilosec® (omeprazole) — 20 mg Protonix® (pantoprazole) — 40 mg
Antiarrhythmics: amiodarone	Unknown	Coadministration with amiodarone may result in serious bradycardia. Coadministration is not recommended; if coadministration is required, cardiac monitoring is recommended.
Antiarrhythmics: digoxin	↑ digoxin	Coadministration with digoxin may increase the concentration of digoxin. Monitor therapeutic concentration of digoxin during coadministration.
Anticonvulsants: carbamazepine, phenytoin,	↓ ledipasvir ↓ sofosbuvir ↓ GS-331007	Coadministration with carbamazepine, phenytoin, phenobarbital, or oxcarbazepine may decrease the concentration of ledipasvir and sofosbuvir, leading to reduced

Concomitant Drug Class: Drug Name	Effect on Concentration	Recommendations
phenobarbital, oxcarbazepine	(metabolite)	therapeutic effect of Harvoni®. Coadministration is not recommended.
Antimycobacterial: rifabutin, rifampin, rifapentine	↓ ledipasvir ↓ sofosbuvir ↓ GS-331007 (metabolite)	Coadministration with rifabutin or rifapentine may decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of Harvoni®. Coadministration is not recommended. Coadministration with rifampin, a P-gp inducer, is not recommended.
Tenofovir disoproxil fumarate	↑ tenofovir	Avoid Harvoni® use if CrCl<60 mL/min. This warning does not apply to tenofovir alafenamide e.g., Genvoya® (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide) or Odefsey® (emtricitabine/rilpivirine/tenofovir alafenamide).
Regimens containing BOTH tenofovir AND an HIV protease inhibitor/ritonavir atazanavir/ritonavir + emtricitabine/tenofovir darunavir/ritonavir + emtricitabine/tenofovir lopinavir/ritonavir + emtricitabine/tenofovir	↑ tenofovir	The safety of increased tenofovir concentrations in the setting of Harvoni® and a HIV protease inhibitor/ritonavir has not been established. Consider alternative HCV or antiretroviral therapy to avoid increases in tenofovir exposures. If coadministration is necessary, monitor for tenofovir-associated adverse reactions.
Stribild® (elvitegravir, cobicistat, emtricitabine, and tenofovir)	↑ tenofovir	The safety of increased tenofovir concentrations in the setting of Harvoni® and the combination of elvitegravir, cobicistat, emtricitabine and tenofovir has not been established. Coadministration is not recommended. Consider Genvoya® (elvitegravir/cobicistat/ emtricitabine/tenofovir alafenamide) as a safe alternative.
HMG-CoA Reductase Inhibitors: rosuvastatin	↑ rosuvastatin	Coadministration may increases risk of myopathy, including rhabdomyolysis. Coadministration with rosuvastatin is not recommended.
Herbal Supplements: St. John's wort	↓ ledipasvir ↓ sofosbuvir ↓ GS-331007 (metabolite)	Coadministration of Harvoni® with St. John's wort, a P-gp inducer is not recommended.
Aptivus® (tipranavir)/ritonavir	↓ ledipasvir ↓ sofosbuvir ↓ GS-331007 (metabolite)	Coadministration with tipranavir/ritonavir may decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of Harvoni®. Coadministration is not recommended.

Table 10. Drug Interactions with dasabuvir/ombitasvir/paritaprevir/ritonavir (Not All Inclusive)

Concomitant Drug Class: Drug Name	Effect on Concentration	Recommendations
Antipsychotic		
Quetiapine	↑ quetiapine	Consider alternative anti-HCV therapy to avoid increases in quetiapine exposures. If coadministration is necessary, reduce the quetiapine dose to 1/6th of the current dose and monitor for quetiapine adverse reactions.
α-1-adrenoreceptor antagonist		
Alfuzosin	-	Contraindicated. Potential for hypotension.
Anticonvulsants		
Carbamazepine, phenytoin,	↓ Viekira Pak/	Contraindicated. Loss of Viekira Pak®/ Viekira

Concomitant Drug Class: Drug Name	Effect on Concentration	Recommendations
phenobarbital, oxcarbazepine	Viekira XR®	XR® therapeutic activity.
Antihyperlipidemic agents		
Gemfibrozil	↑ dasabuvir x 10-fold	Contraindicated. Increased risk of QT interval prolongation.
Lovastatin	-	Contraindicated. Potential for rhabdomyolysis.
Rosuvastatin	↑ rosuvastatin	Rosuvastatin dose not to exceed 10 mg/day.
Simvastatin	-	Contraindicated. Potential for rhabdomyolysis.
Pravastatin	↑ pravastatin	Pravastatin dose not to exceed 40 mg/day.
Antifungals		
Ketoconazole	↑ ketoconazole	Limit ketoconazole dose to 200 mg/day.
Voriconazole	↓ voriconazole	Coadministration is not recommended unless benefit-to-risk ratio justifies the use of voriconazole.
Antimycobacterial		
Rifampin	↓ Viekira Pak®/ Viekira XR®	Contraindicated. Loss of Viekira Pak®/ Viekira XR® therapeutic activity.
Ergot derivatives		
Ergotamine, dihydroergotamine, ergonovine, methylergonovine	↑ ergot derivatives	Contraindicated. Risk of ergot toxicity (vasospasm/tissue ischemia) with ritonavir.
Ethinyl estradiol-containing products (e.g., contraceptives)		
Ethinyl estradiol	-	Contraindicated. Potential for ALT elevations.
Herbal product		
St. John's Wort	↓ Viekira Pak®/ Viekira XR®	Contraindicated. Loss of Viekira Pak®/ Viekira XR® therapeutic activity.
HIV-antiviral agents		
Aptivus® (tipranavir)/ritonavir	Unknown	Coadministration is not recommended by AASLD/IDSA.
Efavirenz-containing products	-	Contraindicated. Potential for LFT elevations.
Elvitegravir/cobicistat/ emtricitabine/tenofovir (disoproxil fumarate or alafenamide)	Unknown	Coadministration is not recommended by AASLD/IDSA.
Reyataz (atazanavir)/ritonavir once daily	↑ paritaprevir	Atazanavir 300 mg (without ritonavir) should only be given in the morning.
Prezista (darunavir)/ritonavir	↓ darunavir	Coadministration is not recommended.
Kaletra (lopinavir/ritonavir)	↑ paritaprevir	Coadministration is not recommended.
Intelence® (etravirine)	Unknown	Coadministration is not recommended by AASLD/IDSA.
Nevirapine	Unknown	Coadministration is not recommended by AASLD/IDSA.
Rilpivirine-containing products (e.g., Edurant or Complera)	↑ rilpivirine	Coadministration is not recommended due to potential for QT interval prolongation.
Long acting β-adrenergic agonist		
Serevent Discus (salmeterol) Advair (fluticasone/salmeterol)	↑ salmeterol	Coadministration is not recommended due to increased risk of QT interval prolongation.
Neuroleptics		
Pimozide	-	Contraindicated. Potential for arrhythmia.
Phosphodiesterase-5 (PDE5) inhibitor		
Revatio (sildenafil)	-	Contraindicated. Potential for sildenafil side effects (visual changes, hypotension, syncope)
Proton Pump Inhibitors		
Omeprazole	↓ omeprazole	Consider increasing omeprazole dose if symptoms are inadequately controlled; avoid use of omeprazole doses >40 mg/day.

Concomitant Drug Class: Drug Name	Effect on Concentration	Recommendations
Sedatives/hypnotics		
Triazolam; oral midazolam	↑ benzodiazepines	Contraindicated. Potential for serious/ life threatening events e.g., respiratory depression.

Table 11. Drug Interactions with sofosbuvir/velpatasvir (Not All Inclusive)

Concomitant Drug Class: Drug Name	Effect on Concentration	Recommendations
H_2-receptor antagonists: famotidine	↓ velpatasvir	H_2-receptor antagonist doses greater than famotidine 40 mg twice daily (or equivalent H_2-receptor antagonist) may decrease ledipasvir concentration. **H_2 antagonist** / **Comparable dose** Tagamet® (cimetidine) / 400 mg to 800 mg twice daily Pepcid® (famotidine) / 40 mg twice daily Axid® (nizatidine) / 300 mg twice daily Zantac® (ranitidine) / 150 mg four times daily
Proton-pump inhibitors (PPI): such as omeprazole	↓ velpatasvir	Coadministration of omeprazole or other PPIs is not recommended. If coadministration is medical necessary, administer Epclusa® (sofosbuvir/velpatasvir) with food four hours before omeprazole 20 mg. Use with other PPIs has not been studied. ***If use with a PPI at a dose exceeding omeprazole 20 mg/day is requested, PA should address whether discontinuing PPI or using omeprazole 20 mg once daily is an option.*** **Proton-pump inhibitor** / **Comparable dose** Aciphex® (rabeprazole) / 20 mg Dexilant® (dexlansoprazole) / 30 mg Nexium® (esomeprazole) / 20 mg Prevacid® (lansoprazole) / 30 mg Prilosec® (omeprazole) / 20 mg Protonix® (pantoprazole) / 40 mg
Antiarrhythmics: amiodarone	Unknown	Coadministration with amiodarone may result in serious bradycardia. Coadministration is not recommended; if coadministration is required, cardiac monitoring is recommended.
Antiarrhythmics: digoxin	↑ digoxin	Coadministration with digoxin may increase the concentration of digoxin. Monitor therapeutic concentration of digoxin during coadministration.
Anticonvulsants: carbamazepine, phenytoin, phenobarbital, oxcarbazepine	↓ sofosbuvir ↓ velpatasvir	Coadministration is not recommended.
Antimycobacterial: rifabutin, rifampin, rifapentine	↓ sofosbuvir ↓ velpatasvir	Coadministration is not recommended.
Efavirenz-containing regimens (Atripla® or Sustiva®)	↓ velpatasvir	Coadministration with efavirenz-containing regimens is not recommended.
Intelence® (etravirine)	Unknown	Coadministration is not recommended by AASLD/IDSA.
Nevirapine	Unknown	Coadministration is not recommended by AASLD/IDSA.
Tenofovir disoproxil fumarate	↑ tenofovir	Avoid Epclusa® use if CrCl<60 mL/min. This warning does not apply to tenofovir alafenamide e.g., Genvoya®

Concomitant Drug Class: Drug Name	Effect on Concentration	Recommendations
		(elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide) or Odefsey® (emtricitabine/rilpivirine/tenofovir alafenamide).
HMG-CoA Reductase Inhibitors: rosuvastatin	↑ rosuvastatin	Coadministration may increases risk of myopathy, including rhabdomyolysis. The dose of rosuvastatin should not exceed 10 mg.
Herbal Supplements: St. John's wort	↓ sofosbuvir ↓ velpatasvir	Coadministration is not recommended.
Aptivus® (tipranavir)/ritonavir	↓ sofosbuvir ↓ velpatasvir	Coadministration is not recommended.

Table 12. Drug Interactions with elbasvir/grazoprevir (Not All Inclusive)

Concomitant Drug Class: Drug Name	Effect on Concentration	Recommendations
Antibiotics		
Nafcillin	↓ elbasvir ↓ grazoprevir	Reduced therapeutic activity of HCV regimen; co-administration is not recommended.
Anticonvulsants		
Phenytoin, carbamazepine	↓ elbasvir ↓ grazoprevir	Loss of therapeutic activity of HCV regimen; contraindicated.
Antifungals		
Ketoconazole	↑ elbasvir ↑ grazoprevir	Concomitant use with systemic ketoconazole increases grazoprevir exposure and may increase the overall risk of hepatotoxicity; coadministration is not recommended.
Antimycobacterials		
Rifampin	↓ elbasvir ↓ grazoprevir	Loss of therapeutic activity of HCV regimen; contraindicated.
Endothelin Antagonists		
Bosentan	↓ elbasvir ↓ grazoprevir	Reduced therapeutic activity of HCV regimen; co-administration is not recommended.
Herbal products		
St. John's Wort (Hypericum perforatum)	↓ elbasvir ↓ grazoprevir	Loss of therapeutic activity of HCV regimen; contraindicated.
HIV Medications		
Atazanavir, darunavir, lopinavir, saquinavir, tipranavir	↑ grazoprevir	May increase the risk of ALT elevations due to a significant increase in grazoprevir plasma concentrations caused by OATP1B1/3 inhibition. Contraindicated.
Efavirenz	↓ elbasvir ↓ grazoprevir	Loss of therapeutic activity of HCV regimen; contraindicated.
Elvitegravir/cobicistat/ emtricitabine/tenofovir (disoproxil fumarate or alafenamide)	↑ elbasvir ↑ grazoprevir	Increased concentrations of elbasvir and grazoprevir. Co-administration is not recommended.
Etravirine	↓ elbasvir ↓ grazoprevir	Reduced therapeutic activity of HCV regimen; co-administration is not recommended.
Nevirapine	Unknown	Coadministration is not recommended by AASLD/IDSA.
HMG-CoA Reductase Inhibitors		
Atorvastatin	↑ atorvastatin	Co-administration increases atorvastatin levels. Atorvastatin dose should not exceed 20 mg/day.
Fluvastatin, lovastatin, simvastatin	↑ fluvastatin, ↑ lovastatin,	Co-administration has not been studied but may increase the concentrations of these statins. Closely

Concomitant Drug Class: Drug Name	Effect on Concentration	Recommendations
	↑ simvastatin	monitor for statin-associated adverse events such as myopathy and use the lowest necessary dose.
Rosuvastatin	↑ rosuvastatin	Co-administration increases rosuvastatin levels. Rosuvastatin dose should not exceed 10 mg/day.
Immunosuppressants		
Cyclosporine	↑ grazoprevir	May increase the risk of ALT elevations due to a significant increase in grazoprevir plasma concentrations caused by OATP1B1/3 inhibition. Contraindicated.
Tacrolimus	↑ tacrolimus	Frequent monitoring of tacrolimus whole blood concentrations, changes in renal function, and tacrolimus-associated adverse events upon the initiation of co-administration is recommended.
Wakefulness-Promoting Agents		
Modafinil	↓ elbasvir ↓ grazoprevir	Reduced therapeutic activity of HCV regimen; co-administration is not recommended.

Table 13. Drug Interactions with ombitasvir/paritaprevir/ritonavir (Not All Inclusive)

Concomitant Drug Class: Drug Name	Effect on Concentration	Recommendations
Antiarrhythmics		
Digoxin	↑ digoxin	Decrease digoxin dose by 30-50%. Appropriate monitoring of serum digoxin levels is recommended.
Antipsychotic		
Quetiapine	↑ quetiapine	Consider alternative anti-HCV therapy to avoid increases in quetiapine exposures. If coadministration is necessary, reduce the quetiapine dose to 1/6th of the current dose and monitor for quetiapine adverse reactions.
α-1-adrenoreceptor antagonist		
Alfuzosin	-	Contraindicated. Potential for hypotension.
Anticonvulsants		
Carbamazepine, phenytoin, phenobarbital, oxcarbazepine	↓ Technivie	Contraindicated. Loss of Technivie therapeutic activity.
HMG-CoA reductase inhibitors		
Lovastatin	-	Contraindicated. Potential for rhabdomyolysis.
Simvastatin	-	Contraindicated. Potential for rhabdomyolysis.
Pravastatin	↑ pravastatin	Pravastatin dose not to exceed 40 mg/day.
Antifungals		
Ketoconazole	↑ ketoconazole	Limit ketoconazole dose to 200 mg/day.
Voriconazole	↓ voriconazole	Coadministration is not recommended unless benefit-to-risk ratio justifies the use of voriconazole.
Antimycobacterial		
Rifampin	↓ Technivie	Contraindicated. Loss of Technivie therapeutic activity.
Ergot derivatives		
Ergotamine, dihydroergotamine, ergonovine, methylergonovine	↑ ergot derivatives	Contraindicated. Risk of ergot toxicity (vasospasm/tissue ischemia) with ritonavir component.
Ethinyl estradiol-containing products (e.g., contraceptives)		
Ethinyl estradiol	-	Contraindicated. Potential for ALT elevations.
Herbal product		

Concomitant Drug Class: Drug Name	Effect on Concentration	Recommendations
St. John's Wort	↓ Technivie	Contraindicated. Loss of Technivie therapeutic activity.
HIV-antiviral agents		
Efavirenz	-	Contraindicated. Potential for LFT elevations.
Reyataz (atazanavir) with or without ritonavir	↑ paritaprevir	Coadministration is not recommended.
Prezista (darunavir)/ritonavir	↓ darunavir	Technivie and darunavir 800 mg (without ritonavir) should be taken at the same time.
Kaletra (lopinavir/ritonavir)	↑ paritaprevir	Coadministration is not recommended.
Rilpivirine-containing products (e.g., Edurant or Complera)	↑ rilpivirine	Coadministration is not recommended due to potential for QT interval prolongation.
Long acting β-adrenergic agonist		
Serevent Discus (salmeterol) Advair (fluticasone/salmeterol)	↑ salmeterol	Coadministration is not recommended due to increased risk of QT interval prolongation.
Neuroleptics		
Pimozide	-	Contraindicated. Potential for arrhythmia.
Phosphodiesterase-5 (PDE5) inhibitor		
Revatio (sildenafil)	-	Contraindicated. Potential for sildenafil side effects (visual changes, hypotension, syncope)
Proton Pump Inhibitors		
Omeprazole	↓ omeprazole	Consider increasing omeprazole dose if symptoms are inadequately controlled; avoid use of omeprazole doses >40 mg/day.
Sedatives/hypnotics		
Triazolam; oral midazolam	↑ benzodiazepines	Contraindicated. Potential for serious/ life threatening events e.g., respiratory depression.

Table 14. Drug Interactions with glecaprevir and pibrentasvir (Not All Inclusive)

Concomitant Drug Class: Drug Name	Effect on Concentration	Recommendations
Antiarrhythmics: Digoxin	↑ digoxin	Measure serum digoxin concentrations before initiating glecaprevir/pibrentasvir. Decrease digoxin dose by approximately 50% or by modifying the dosing frequency and continue monitoring.
Anticoagulants: dabigatran etexilate	↑ dabigatran	Modify dabigatran dose per prescribing information in the setting of renal impairment.
Anticonvulsants: carbamazepine	↓ glecaprevir ↓ pibrentasvir	Coadministration may lead to reduced antiviral efficacy and is not recommended.
Antimycobacterial: rifampin	↓ glecaprevir ↓ pibrentasvir	Coadministration is contraindicated due to potential loss of antiviral efficacy.
Ethinyl estradiol-containing products: oral contraceptives	-	Coadministration may increase the risk of alanine ALT and is not recommended.
Herbal Supplements: St. John's wort	↓ glecaprevir ↓ pibrentasvir	Coadministration may lead to reduced antiviral efficacy and is not recommended.
Antiretrovirals: atazanavir	↑ glecaprevir ↑ pibrentasvir	Coadministration is contraindicated due to increased risk of ALT elevations.
darunavir, lopinavir, ritonavir	↑ glecaprevir ↑ pibrentasvir	Coadministration is not recommended.
efavirenz	↓ glecaprevir	Coadministration may lead to reduced antiviral

Concomitant Drug Class: Drug Name	Effect on Concentration	Recommendations
	↓ pibrentasvir	efficacy and is not recommended.
HMG-CoA Reductase Inhibitors: atorvastatin, fluvastatin, lovastatin simvastatin pravastatin rosuvastatin fluvastatin, pitavastatin	↑ atorvastatin ↑ lovastatin ↑ simvastatin ↑ pravastatin ↑ rosuvastatin ↑ fluvastatin ↑ pitavastatin	Coadministration may increase the concentration of atorvastatin, lovastatin, and simvastatin, leading to an increased risk of myopathy, including rhabdomyolysis. Coadministration is not recommended. Coadministration may increase the concentration of pravastatin, leading to increased risk of myopathy, including rhabdomyolysis. Reduce pravastatin dose by 50%. Coadministration may significantly increase the concentration of rosuvastatin, leading to increased risk of myopathy, including rhabdomyolysis. Rosuvastatin dose should not exceed 10 mg. Coadministration may increase the concentrations of fluvastatin and pitavastatin, leading to increased risk of myopathy, including rhabdomyolysis. Use the lowest necessary statin dose based on a risk/benefit assessment.
Immunosuppressants: cyclosporine	↑ glecaprevir ↑ pibrentasvir	Coadministration is not recommended in patients requiring stable cyclosporine doses >100 mg/day.

Abbreviations: ALT=aminotransferase elevations

Table15. Drug Interactions with sofosbuvir/velpatasvir/voxilaprevir (Not All Inclusive)

Concomitant Drug Class: Drug Name	Effect on Concentration	Recommendations
Antacids (e.g., aluminum and magnesium hydroxide)	↓ velpatasvir	It is recommended to separate antacid and Vosevi® (sofosbuvir/velpatasvir/voxilaprevir) administration by four hours.
H_2-receptor antagonists (e.g., famotidine)	↓ velpatasvir	H_2-receptor antagonists may be administered simultaneously with or staggered from Vosevi® (sofosbuvir/velpatasvir/voxilaprevir) at a dose that does not exceed doses comparable to famotidine 40 mg twice daily.
PPIs (e.g., omeprazole)	↓ velpatasvir	Omeprazole 20 mg can be administered with Vosevi® (sofosbuvir/velpatasvir/voxilaprevir). Use with other proton pump-inhibitors has not been studied.
Antiarrhythmics: amiodarone	Unknown	Coadministration with of amiodarone may result in serious symptomatic bradycardia and is not recommended; if coadministration is required, cardiac monitoring is recommended.
Antiarrhythmics: digoxin	↑ digoxin	Coadministration with digoxin may increase the concentration of digoxin. Monitor therapeutic concentration of digoxin during coadministration.
Anticoagulants: dabigatran etexilate	↑ dabigatran	Coadministration necessitates clinical monitoring of dabigatran.
Anticonvulsants: carbamazepine, phenytoin, phenobarbital,	↓ sofosbuvir ↓ velpatasvir ↓ voxilaprevir	Coadministration is not recommended.

Concomitant Drug Class: Drug Name	Effect on Concentration	Recommendations
oxcarbazepine		
Antimycobacterial: rifampin	↓ sofosbuvir ↓ velpatasvir ↑ voxilaprevir (single dose) ↓ voxilaprevir (multiple dose)	Coadministration with rifampin is contraindicated.
rifabutin, rifapentine	↓ sofosbuvir ↓ velpatasvir ↓ voxilaprevir	Coadministration is not recommended.
Antiretrovirals: atazanavir lopinavir	↑ voxilaprevir	Coadministration with atazanavir- or lopinavir-containing regimens is not recommended.
tipranavir/ritonavir	↓ sofosbuvir ↓ velpatasvir	Coadministration with tipranavir/ritonavir is not recommended; the effect on voxilaprevir is unknown.
efavirenz	↓ velpatasvir ↓ voxilaprevir	Coadministration with efavirenz-containing regimens is not recommended.
tenofovir disoproxil fumarate	↑ tenofovir	Monitor for tenofovir-associated adverse reactions.
Herbal Supplements: St. John's wort	↓ sofosbuvir ↓ velpatasvir ↓ voxilaprevir	Coadministration is not recommended.
HMG-CoA Reductase Inhibitors: pravastatin	↑ pravastatin	Coadministration increases the concentration of pravastatin, which is associated with increased risk of myopathy, including rhabdomyolysis. Pravastatin dose should not exceed 40 mg.
rosuvastatin	↑ rosuvastatin	Coadministration may significantly increase the concentration of rosuvastatin, which is associated with increased risk of myopathy, including rhabdomyolysis. Coadministration is not recommended.
pitavastatin	↑ pitavastatin	Coadministration may increase the concentration of pitavastatin and is not recommended, due to an increased risk of myopathy, including rhabdomyolysis.
atorvastatin fluvastatin lovastatin simvastatin	↑ atorvastatin ↑ fluvastatin ↑ lovastatin ↑ simvastatin	Coadministration may increase the concentrations of atorvastatin, fluvastatin, lovastatin, and simvastatin, which may increase the risk of myopathy, including rhabdomyolysis. It is recommended to use the lowest necessary statin dose based on a risk/benefit assessment.
Immunosuppressants: cyclosporine	↑ voxilaprevir	Coadministration has been shown to substantially increase the plasma concentration of voxilaprevir, the safety of which has not been established. Coadministration is not recommended.

VI. Adverse Drug Events

The most common adverse drug events reported with the HCV antivirals are listed in Tables 16 and 17. The boxed warning is in Table 18.

Table 16. Adverse Drug Events (%) Reported with the Single-Entity HCV Antivirals[14]

Adverse Events	Daclatasvir	Simeprevir	Sofosbuvir
Central Nervous System			
Chills	-	-	2 to 17
Dizziness	-	16	-
Fatigue	14	25	30 to 59
Headache	14	21	24 to 36
Insomnia	-	14	-
Irritability	-	-	10 to 13
Dermatologic			
Photosensitivity	-	5	-
Pruritus	-	22	11 to 27
Rash	-	28	8 to 18
Gastrointestinal			
Appetite decreased	-	-	18
Diarrhea	5	16	9 to 12
Increased serum lipase	-	-	≤2
Nausea	8	22	22 to 34
Hematologic			
Anemia	-	-	6 to 21
Decreased hemoglobin	-	-	2 to 23
Neutropenia	-	-	1 to 17
Thrombocytopenia	-	-	≤1
Musculoskeletal			
Myalgia	-	16	6 to 14
Weakness	-	-	5 to 21
Other			
Dyspnea	-	12	-
Fever	-	-	4 to 18
Flu-like symptoms	-	-	6 to 16
Hyperbilirubinemia	-	<50	3
Increased creatine phosphokinase	-	-	1 to 2
Increased serum alkaline phosphatase	-	<4	-
Increased serum lipase	2	-	-

✓ Percent not specified
- Event not reported

Table 17. Adverse Drug Events (%) Reported with the Combination Product HCV Antivirals[14]

Adverse Events	Dasabuvir, ombitasvir, paritaprevir, and ritonavir	Elbasvir and grazoprevir	Glecaprevir and pibrentasvir	Ledipasvir and sofosbuvir	Ombitasvir, paritaprevir, and ritonavir	Sofosbuvir and velpatasvir	Sofosbuvir, velpatasvir, and voxilaprevir
Central Nervous System							
Anxiety	-	1	-	-	-	-	-
Asthenia	4 to 14	-	7	-	-	5	4 to 6
Depression	-	1	-	-	-	-	-
Dizziness	-	2 to 3	-	-	-	-	-
Fatigue	34 to 50	5 to 11	11 to 14	13 to 18	7	≥10	17 to 19
Headache	16 to 44	≤11	6 to 17	11 to 17	-	≥10	21 to 23
Insomnia	5 to 26	3 to 5	-	3 to 6	5	5	3 to 6

Adverse Events	Dasabuvir, ombitasvir, paritaprevir, and ritonavir	Elbasvir and grazoprevir	Glecaprevir and pibrentasvir	Ledipasvir and sofosbuvir	Ombitasvir, paritaprevir, and ritonavir	Sofosbuvir and velpatasvir	Sofosbuvir, velpatasvir, and voxilaprevir
Irritability	10	1 to 2	-	-	-	✔	-
Dermatologic							
Alopecia	-	1	-	-	-	-	-
Night sweats	-	2	-	-	-	-	-
Pruritus	7 to 18	≤2	17	-	5	-	-
Rash	7 to 24	-	-	-	-	✔	-
Gastrointestinal							
Abdominal pain	-	2	-	-	-	-	-
Appetite decreased	-	2	-	-	-	-	-
Constipation	-	2	-	-	-	-	-
Diarrhea	-	2 to 5	3 to 7	3 to 7	-	✔	13 to 14
Dyspepsia	-	2	-	-	-	-	-
Flatulence	-	2	-	-	-	-	-
Increased serum lipase	-	-	-	≤3	-	-	-
Mouth ulceration	-	-	-	-	-	-	-
Nausea	8 to 22	5 to 11	6 to 12	6 to 9	9	9	10 to 13
Stomatitis	-	-	-	-	-	-	-
Vomiting	-	1 to 2	-	-	-	-	-
Xerostomia	-	1 to 2	-	-	-	-	-
Hematologic							
Decreased hemoglobin	<1 to 29	-	-	-	-	-	-
Musculoskeletal							
Arthralgia	-	≤2	-	-	-	-	-
Muscle spasm	21	-	-	-	-	-	-
Myalgia	-	2	-	-	-	-	-
Weakness	4 to 14	4	-	-	25	-	-
Other							
Cough	11 to 32	-	-	-	-	-	-
Dyspnea	✔	-	-	-	-	-	-
Hyperbilirubinemia	2 to 15	≤2	-	≤3	-	-	-
Increased alanine aminotransferase	1	≤1	-	-	-	-	-
Increased creatine phosphokinase	-	2	-	✔	-	-	-
Scleral Icterus	10	-	-	-	-	-	-
Tinnitus	-	2	-	-	-	-	-

✔ Percent not specified
- Event not reported

Table 18. Boxed Warning for the HCV Antivirals[16]

WARNING
WARNING: RISK OF HEPATITIS B VIRUS REACTIVATION IN PATIENTS COINFECTED WITH HCV AND HBV Test all patients for evidence of current or prior hepatitis B virus (HBV) infection before initiating treatment with HCV Antiviral agents. HBV reactivation has been reported in HCV/HBV coinfected patients who were undergoing or had completed treatment with HCV direct-acting antivirals and were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure, and death. Monitor HCV/HBV coinfected patients for hepatitis flare or HBV reactivation during HCV treatment and post-treatment followup. Initiate appropriate management for HBV infection as clinically indicated.

VII. Dosing and Administration

The usual dosing regimens for the HCV antivirals are listed in Table 19.

Table 19. Usual Dosing Regimens for the HCV Antivirals[1-11]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Daclatasvir	Hepatitis C, chronic, genotype 1 Tablet: 60 mg once daily with sofosbuvir for 12 weeks; add on ribavirin if decompensated cirrhosis (B or C) or post-transplant Hepatitis C, chronic, genotype 3 Tablet: 60 mg once daily with sofosbuvir for 12 weeks; add on ribavirin if cirrhosis (A, B, or C) or post-transplant	Safety and efficacy in children have not been established	Tablet: 30 mg 60 mg 90 mg
Simeprevir	Hepatitis C, chronic, genotype 1: Capsule: 150 mg orally once daily in combination with sofosbuvir for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis) Hepatitis C, chronic, genotype 1 or 4: Capsule: 150 mg once daily in combination with peginterferon alfa and ribavirin for at least 12 weeks	Safety and efficacy in children have not been established	Capsule: 150 mg
Sofosbuvir	Hepatitis C, chronic, genotype 1: Tablet: 400 mg once daily for 12 weeks (in combination with peginterferon alfa and ribavirin) or 24 weeks (in combination with ribavirin alone if not eligible for peginterferon alfa) Hepatitis C, chronic, genotype 2: Tablet: 400 mg once daily for 12 weeks (in combination with ribavirin) Hepatitis C, chronic, genotype 3: Tablet: 400 mg once daily for 24 weeks (in combination with ribavirin) Hepatitis C, chronic, genotype 4: Tablet: 400 mg once daily for 12 weeks (in combination with peginterferon alfa and ribavirin)	Hepatitis C, chronic, genotype 2 in patients ≥12 years of age or weighing ≥35 kg: Tablet: 400 mg once daily for 12 weeks (in combination with ribavirin) Hepatitis C, chronic, genotype 3 in patients ≥12 years of age or weighing ≥35 kg: Tablet: 400 mg once daily for 24 weeks (in combination with ribavirin)	Tablet: 400 mg
Combination Products			
Dasabuvir Sodium, Ombitasvir, Paritaprevir, and Ritonavir	Hepatitis C, chronic, genotype 1: Dose pack: Two ombitasvir, paritaprevir, ritonavir tablets once daily (in the morning) and one dasabuvir tablet twice daily (morning and evening) with a meal; the duration of treatment and use with or without ribavirin is based on viral subtype, prior response status, and presence of cirrhosis (ranging from a total treatment time of 12 to 24 weeks) Extended release tablet: Three tablets once daily; the duration of treatment and use with or without ribavirin is based on viral subtype, prior response status, and presence of	Safety and efficacy in children have not been established	Dose pack (Viekira Pak®): 250 mg tablet; 12.5-75-50 mg tablet Extended release tablet (Viekira XR®): 200-8.33-50-33.33 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	cirrhosis (ranging from a total treatment time of 12 to 24 weeks)		
Elbasvir and grazoprevir	Hepatitis C, chronic, genotype 1: Genotype 1a: Treatment-naïve or prior peginterferon alfa plus ribavirin failure without baseline NS5A polymorphisms Tablet: 50 mg-100 mg once daily for 12 weeks Genotype 1a: Treatment-naïve or prior peginterferon alfa plus ribavirin failure with baseline NS5A polymorphisms Tablet: 50 mg-100 mg once daily in combination with ribavirin for 16 weeks Genotype 1b: Treatment-naïve or prior peginterferon alfa plus ribavirin failure Tablet: 50 mg-100 mg once daily for 12 weeks Genotype 1a or 1b: Prior HCV protease inhibitor/peginterferon alfa/ribavirin failure Tablet: 50 mg-100 mg once daily in combination with ribavirin for 12 weeks Hepatitis C, chronic, genotype 4: Treatment-naïve Tablet: 50 mg-100 mg once daily for 12 weeks Prior peginterferon alfa plus ribavirin failure Tablet: 50 mg-100 mg once daily in combination with ribavirin for 16 weeks	Safety and efficacy in children have not been established	Tablet: 50-100 mg
Glecaprevir and pibrentasvir	Treatment-naïve patients with HCV genotype 1 through 6 Tablet: Three tablets once daily for 8 weeks (no cirrhosis) or 12 weeks (compensated cirrhosis) Treatment-experienced (PRS) patients with HCV genotype 1, 2, 4, 5, or 6 Tablet: Three tablets once daily for 8 weeks (no cirrhosis) or 12 weeks (compensated cirrhosis) Treatment-experienced (PRS) patients with HCV genotype 3 with or without compensated cirrhosis Tablet: Three tablets once daily for 16 weeks Treatment-experienced (NS5A inhibitor without an NS3/4A PI) patients with HCV genotype 1 with or without compensated cirrhosis Tablet: Three tablets once daily for 16 weeks	Safety and efficacy in children have not been established	Tablet: 100-40 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Treatment-experienced (NS3/4A protease inhibitor without an NS5A inhibitor) patients with HCV genotype 1 with or without compensated cirrhosis Tablet: Three tablets once daily for 12 weeks		
Ledipasvir and sofosbuvir	**Hepatitis C, chronic, genotype 1:** Tablet: 90 mg-400 mg once daily for eight, 12, or 24 weeks with or without ribavirin based on prior treatment history, cirrhosis status and baseline viral load as follows: Treatment-naïve without cirrhosis *Baseline HCV RNA <6 million IU/mL* 8 or 12 weeks *Baseline HCV RNA ≥6 million IU/mL* 12 weeks Treatment-naïve with cirrhosis OR treatment-experienced* without cirrhosis 12 weeks Treatment-experienced* with cirrhosis 12 weeks (with ribavirin) or 24 weeks (without ribavirin) **Hepatitis C, chronic, genotype 4, 5, or 6:** Treatment-naïve or treatment-experienced* with or without cirrhosis Tablet: 90 mg-400 mg once daily for 12 weeks with or without ribavirin *prior failure of peginterferon alfa plus ribavirin (with or without HCV protease inhibitor)	Hepatitis C, chronic, genotype 1 in patients ≥12 years of age or weighing ≥35 kg: Tablet: 90-400 mg once daily for 12 or 24 weeks based on prior treatment history and cirrhosis status Hepatitis C, chronic, genotypes 4, 5, or 6 in patients ≥12 years of age or weighing ≥35 kg: Tablet: 90-400 mg once daily for 12 weeks	Tablet: 90-400 mg
Ombitasvir, paritaprevir, and ritonavir	Genotype 4, Treatment-naïve or treatment-experienced (without cirrhosis or with compensated cirrhosis): Tablet: Two ombitasvir/paritaprevir/ritonavir 12.5/75/50 mg tablets once daily for 12 weeks	Safety and efficacy in children have not been established	Tablet: 12.5-75-50 mg
Sofosbuvir and velpatasvir	Hepatitis C, chronic, genotype 1, 2, 3, 4, 5, and 6: Tablet: One tablet once daily for 12 weeks; add on ribavirin in patients with decompensated cirrhosis (B and C)	Safety and efficacy in children have not been established	Tablet: 400-100 mg
Sofosbuvir, velpatasvir, and voxilaprevir	Chronic HCV infection in patients with genotype 1 through 6 without cirrhosis and with compensated cirrhosis (Child-Pugh A) who have been previously treated with a regimen containing an NS5A inhibitor* Tablet: 400 mg/100 mg/100 mg once daily for 12 weeks Chronic HCV infection in patients with genotype 1a or 3 without cirrhosis and with	Safety and efficacy in children have not been established	Tablet: 400-100-100 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	compensated cirrhosis (Child-Pugh A) who have been previously treated with a regimen containing sofosbuvir without an NS5A inhibitor† Tablet: 400 mg/100 mg/100 mg once daily for 12 weeks		

PRS=Prior treatment experience with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, but no prior treatment experience with an HCV NS3/4A PI or NS5A inhibitor.

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the HCV antivirals are summarized in Table 20.

Table 20. Comparative Clinical Trials with the HCV Antivirals

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Treatment of Chronic Hepatitis C: Treatment-Naïve Patients				
Kwo et al.[17] (2010) SPRINT-1 Peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 800 to 1,400 mg/day for 48 weeks (PR48) vs peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 800 to 1,400 mg/day for 4 weeks, followed by peginterferon alfa-2b, ribavirin, and boceprevir 800 mg 3 times a day for 24 weeks (PRB24) vs peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 800 to 1,400 mg/day for 4 weeks, followed by peginterferon alfa-2b, ribavirin, and boceprevir 800 mg 3 times a day for 44 weeks (PRB44) vs	MC, OL, RCT Patients 18 to 60 years of age with hepatitis C genotype 1 who were treatment-naïve	N=595 72 weeks	Primary: SVR and viral breakthrough Secondary: Not reported	Primary: All four boceprevir groups had significantly better SVR than the PR48 control group. In the 28-week treatment groups, the SVR was 56% in the PR4/PRB24 group (P=0.005 vs control) and 54% in the PRB28 group (P=0.013 vs control). In the 48-week treatment groups, the SVR was 75% in the PR4/PRB44 group (P<0.0001 vs control) compared to 67% in the PRB48 group (P<0.0001 vs control). There were significantly lower relapse rates in the 48-week treatment groups compared to PR48 control (PRB48, P=0.0079; PR4/PRB44, P=0.0002). Low-dose ribavirin was associated with a high rate of viral breakthrough (27%), and a rate of relapse (22%) similar to control (24%). The rate of breakthrough in the boceprevir lead-in groups was 4% compared to 9% in the boceprevir groups with no lead in (P=0.057). In the 28-week treatment groups, 82% of patients in the PR4/PRB24 group and 74% in the PRB28 group who had rapid virological response achieved SVR. In the 48-week treatment groups, 94% of patients assigned to PR4/PRB44 and 84% assigned to PRB48 who achieved undetectable hepatitis C virus RNA by week four of boceprevir achieved SVR. The most common side effects in the boceprevir group were fatigue, anemia, nausea and headache, which was similar to PR48 control. The rate of dysgeusia and anemia was higher in boceprevir groups

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 800 to 1,400 mg/day plus boceprevir 800 mg 3 times a day for 28 weeks (PRB28) vs peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 800 to 1,400 mg/day plus boceprevir 800 mg 3 times a day for 48 weeks (PRB48) vs peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 400 to 1,000 mg/day for 4 weeks, followed by peginterferon alfa-2b, ribavirin, and boceprevir 800 mg 3 times a day for 48 weeks (PRB48)				than other groups. Treatment discontinuation was nine to 19% in boceprevir studies compared to 8% in the PR48 control group. Secondary: Not reported
Poordad et al.[18] (2011) SPRINT-2 Group 1 (control): Peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 44 weeks vs Group 2 (response-guided therapy): boceprevir 800 mg three times a day plus peginterferon	MC, PC, PG, RCT Patients ≥18 years of age with a history of no previous treatment for HCV infection, weight 40 to 125 kg, chronic infection with HCV genotype 1 and plasma	N=1,097 (N=938 [nonblack], N=159 [black]) 48 weeks (plus 24 weeks of follow up)	Primary: SVR and safety Secondary: Not reported	Primary: Among nonblack patients, the rate of SVR was 40, 67, and 68% in Groups 1, 2 and 3 (P<0.001 vs Group 1 for both Group 2 and 3). The corresponding numbers in black patients were 23, 42 (P=0.04 vs Group 1), and 53% (P=0.004 vs Group 1). Subgroup analyses revealed that at four weeks, 23 and 38% of nonblack and black patients had a decrease of <1 $\log_{10}$ IU/mL in HCV RNA level from baseline, which was associated with lower rates of SVR and higher rates of boceprevir-resistance-associated variants compared to those achieving a decrease of ≥1 $\log_{10}$ IU/mL from baseline. However, regardless of the degree of reduction achieved at week four, patients receiving boceprevir achieved consistently higher rates of SVR compared to patients who received control overall.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 24 weeks, followed by an additional 20 weeks of peginterferon alfa-2b plus ribavirin in detectable HCV RNA levels at any visit from week 8 to 24 vs Group 3 (fixed duration therapy): boceprevir 800 mg three times a day plus peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 44 weeks All patients entered a 4 week lead in period in which peginterferon alfa-2b and ribavirin were administered. The trial consisted of two cohorts enrolling nonblacks and blacks separately. Treatment was considered complete in Group 2 if the HCV RNA level was undetectable from week 8 through week 24 (total duration, 28 weeks). In all 3 treatment groups, treatment was discontinued for all patients with a detectable HCV RNA level at week 24 based on futility rules; these patients then	HCV RNA level ≥10,000 IU/mL			Response rates at the end of therapy (undetectable HCV RNA level at the time that the study therapy was discontinued) were significantly higher with boceprevir-containing regimens compared to the control regimen. Among nonblack patients, viral breakthrough (undetectable HCV RNA level and subsequent occurrence of an HCV RNA level >1,000 IU/mL) occurred in one to two percent of all patients, regardless of treatment regimen. In addition, relapse rates (undetectable HCV RNA level at the end of treatment but a detectable HCV RNA level at some point during the follow up period) were lower with boceprevir compared to control. The numbers of events among black patients were too few to permit comparison between the treatment groups. Adverse events occurred in more than 98% of all patients, with serious adverse events in 9, 11 and 12% of patients in Groups 1, 2 and 3, respectively. There were six deaths during the trial; four deaths in Group 1 and two deaths from boceprevir-containing regimens. Two suicides (one in Group 1 and one in Group 2) were determined to have possibly been related to treatment with peginterferon. Fatigue, headache, and nausea were the most commonly reported adverse events. The incidence of dysgeusia was higher with boceprevir treatment. Anemia was reported in 29 and 49% of patients receiving control and boceprevir, respectively. Overall, 13 and 21% of control- and boceprevir-treated patients required dose reductions because of anemia and erythropoietin was administered in 24 and 43% of patients. Neutropenia and thrombocytopenia also occurred more frequently with boceprevir treatment. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
entered the follow up period.				
Zeuzem et al.[19] (2015) C-EDGE TN **Immediate-treatment group** Elbasvir/grazoprevir 100 mg/50 mg once daily for 12 weeks vs **Deferred-treatment group** placebo (followed by open-label elbasvir/grazoprevir 100 mg/50 mg once daily for 12 weeks)	DB, MC, PC, PG, R Patients >18 years of age with HCV genotype 1, 4 or 6 infection who were treatment-naïve with baseline HCV-RNA levels ≥10,000 IU/mL	N=421 12 weeks	Primary: SVR12 in the immediate-treatment group Secondary: Not reported	Primary: SVR12 was achieved in 95% (299/316) of patients overall. SVR12 rates were 92% (144/157) in patients with genotype 1a infection, 99% (129/131) in those with genotype 1b, 100% (18/18) in those with genotype 4, and 80% (8/10) in those with genotype 6. SVR12 was achieved in 97% (68/70) of cirrhotic patients and 94% (231/246) of noncirrhotic patients. Secondary: Not reported
Rockstroh et al.[20] (2015) C-EDGE COINFECTION Elbasvir/grazoprevir 100 mg/50 mg once daily for 12 weeks	MC, OL, SA Patients >18 years of age with HCV genotype 1, 4 or 6 and HIV-coinfection who were treatment-naïve for all anti-HCV treatments and either treatment-naïve to treatment with ART or on ART (tenofovir or abacavir, and either	N=218 12 weeks	Primary: SVR12 Secondary: Not reported	Primary: SVR12 was achieved by 96.3% (210/218) of patients. SVR12 rates were 96.5% (139/144) in patients with genotype 1a infection, 95.5% (42/44) in those with genotype 1b, 96.4% (27/28) in those with genotype 4, and 100% (2/2) in those with genotype 6. All 35 patients with cirrhosis achieved SVR12. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	emtricitabine or lamivudine plus raltegravir, dolutegravir, and rilpivirine) for at least eight weeks prior to study entry with undetectable HIV levels			
Sulkowski et al.[21] (2015) C-WORTHY **Cohort A** Elbasvir/grazoprevir 100 mg/20 mg once daily plus weight-based ribavirin for 12 weeks (Arm A1; HCV genotype 1a or 1b monoinfected) vs elbasvir/grazoprevir 100 mg/50 mg once daily plus weight-based ribavirin for 12 weeks (Arm A2; HCV genotype 1a or 1b monoinfected) vs elbasvir/grazoprevir 100 mg/50 mg once daily for 12 weeks (Arm A3; HCV genotype 1b monoinfected) **Cohort B**	MC, OL, PG, R Patients >18 years of age with HCV genotype 1 infection, baseline HCV-RNA levels ≥10,000 IU/mL, and weight >50 kg, treatment-naïve and without cirrhosis who were HCV-monoinfected (all arms, except B12 and B13) or HCV/HIV-coinfected (arms B12 and B13 only)	N=218 8 to 12 weeks	Primary: SVR12 Secondary: Not reported	Primary: Among patients in arm B1 (HCV genotype 1a monoinfected, treated with added ribavirin for eight weeks), 80% (24/30) achieved SVR12. Among patients in arms A1, A2, and B2 (HCV genotype 1a or 1b monoinfected, treated with added ribavirin for 12 weeks), 92.9% (79/85) achieved SVR12. Among patients in arms A3 and B3 (HCV genotype 1a monoinfected, treated without ribavirin for 12 weeks), 97.7% (43/44) achieved SVR12. Among patients in arm B12 (HCV genotype 1a or 1b; HIV-coinfected, treated with added ribavirin for 12 weeks), 96.6% (28/29) achieved SVR12. Among patients in arm B13 (genotype 1a or 1b; HIV-coinfected, treated without ribavirin for 12 weeks), 86.7% (26/30) achieved SVR12. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
elbasvir/grazoprevir 100 mg/50 mg once daily plus weight-based ribavirin for 8 weeks (Arm B1; HCV genotype 1a monoinfected) vs elbasvir/grazoprevir 100 mg/50 mg once daily plus weight-based ribavirin for 12 weeks (Arm B2; HCV genotype 1a or 1b monoinfected) vs elbasvir/grazoprevir 100 mg/50 mg once daily for 12 weeks (Arm B3; HCV genotype 1a monoinfected) vs elbasvir/grazoprevir 100 mg/50 mg once daily plus weight-based ribavirin for 12 weeks (Arm B12; genotype 1a or 1b; HIV-coinfected) vs elbasvir/grazoprevir 100 mg/50 mg once daily for 12 weeks (Arm B13; genotype 1a or 1b; HIV-coinfected)				

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Total daily doses of ribavirin were based on bodyweight: 51 to 65 kg, 800 mg/day; 66 to 80 kg, 1,000 mg/day; 81 to 105 kg, 1200 mg/day; and >105 kg to 125 kg, 1,400 mg/day.				
Afdhal et al.[22] (2014) ION 1 Ledipasvir 90 mg and sofosbuvir 400 mg once daily for 12 weeks vs ledipasvir 90 mg and sofosbuvir 400 mg once daily for 12 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 12 weeks vs ledipasvir 90 mg and sofosbuvir 400 mg once daily for 24 weeks vs ledipasvir 90 mg and sofosbuvir 400 mg once daily for 24 weeks and ribavirin 1,000 mg (weight <75	MC, OL, R Patients ≥18 years of age with chronic HCV genotype 1 infection who had not previously received treatment for HCV infection	N=865 12 to 24 weeks	Primary: SVR12 Secondary: Not reported	Primary: The SVR12 rates in all four treatment groups were higher than the historical rate of 60% (P<0.001 for all comparisons). The SVR rates were 99% (95% CI, 96 to 100) in the group that received 12 weeks of ledipasvir/sofosbuvir; 97% (95% CI, 94 to 99) in the group that received 12 weeks of ledipasvir/sofosbuvir with ribavirin; 98% (95% CI, 95 to 99) in the group that received 24 weeks of ledipasvir/sofosbuvir; and 99% (95% CI, 97 to 100) in the group that received 24 weeks of ledipasvir/sofosbuvir with ribavirin. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 24 weeks				
Kowdley et al.[23] (2014) ION 3 Ledipasvir 90 mg and sofosbuvir 400 mg once daily for 8 weeks vs ledipasvir 90 mg and sofosbuvir 400 mg once daily for 8 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 12 weeks vs ledipasvir 90 mg and sofosbuvir 400 mg once daily for 12 weeks	MC, OL, R Patients ≥18 years of age with chronic HCV genotype 1 infection without cirrhosis who had not previously received treatment for HCV infection	N=647 8 to 12 weeks	Primary: SVR12 Secondary: Noninferiority of eight weeks of ledipasvir/ sofosbuvir to the other treatment regimens	Primary: The SVR12 rates in all four treatment groups were higher than the historical rate of 60% (P<0.001 for all comparisons). The SVR12 rate was 94% (95% CI, 90 to 97) with eight weeks of ledipasvir/sofosbuvir, 93% (95% CI, 89 to 96) with eight weeks of ledipasvir/sofosbuvir with ribavirin, and 95% (95% CI, 92 to 98) with 12 weeks of ledipasvir/sofosbuvir. Secondary: Treatment with ledipasvir/sofosbuvir for eight weeks was noninferior to both the 8-week ledipasvir/sofosbuvir + ribavirin treatment arm (treatment difference 0.9%; 95% CI, -3.9 to 5.7%) and the 12-week ledipasvir/sofosbuvir treatment arm (treatment difference -1.4%; 95% CI, -6.4 to 3.6%).
Feld et al.[24] (2014) SAPPHIRE-I ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 12 weeks and dasabuvir 250 mg twice daily for	DB, MC, PC, R Patients 18 to 70 years of age with chronic HCV genotype 1 infection, no cirrhosis, who had not previously received	N=631 12 weeks	Primary: SVR12 Secondary: Normalization of the alanine aminotransferase level, SVR12 by HCV subtype (1a or 1b),	Primary: The SVR12 rate in group A (96.2%; 95% CI, 94.5 to 97.9) was statistically noninferior and superior to the calculated historical control rate of 78% (95% CI, 75 to 80) in treatment-naïve patients without cirrhosis who received telaprevir and PEG/RBV. Secondary: The SVR12 rate was 95.3% (95% CI, 93.0 to 97.6) among patients with HCV genotype 1a infection and 98.0% (95% CI, 95.8 to 100) among those with HCV genotype 1b infection. These rates were statistically superior to the historical control rates in the respective

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
12 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 12 weeks (Group A) vs placebo for 12 weeks of double-blind period followed by active regimen as open-label therapy for 12 weeks (Group B) (ABT-450 is the experimental name for paritaprevir)	treatment for HCV infection, and HCV RNA> 10,000 IU/mL		virologic failure during treatment, and posttreatment relapse	subgroups (72%; 95% CI, 68 to 75 in patients with HCV genotype 1a infection and 80%; 95% CI, 75 to 84 in those with HCV genotype 1b infection). The rate of normalization of the alanine aminotransferase level was 97.0% in group A as compared with 14.9% in group B (P<0.001). Virologic failure during treatment and relapse after treatment occurred in 0.2% and 1.5%, respectively, of the patients in group A.
Ferenci et al.[25] (2014) PEARL-III and PEARL-IV ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 12 weeks and dasabuvir 250 mg twice daily for 12 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 12 weeks	DB, MC, R Patients 18 to 70 years of age with chronic HCV genotype 1b infection (PEARL-III) or HCV genotype 1a infection (PEARL-IV), no cirrhosis, who had not previously received treatment for HCV infection, and HCV RNA>	PEARL-III N=419 12 weeks PEARL-IV N=305 12 weeks	Primary: SVR12 Secondary: Superiority of the SVR12 rate at each group as compared with the historical rate with telaprevir plus PEG/RBV, noninferiority of the SVR12 rate in the groups that did and did not	Primary: In the genotype 1a study, the SVR12 rates were 97.0% (95% CI, 93.7 to 100) in patients who received the regimen with ribavirin and 90.2% (95% CI, 86.2 to 94.3) in patients who received the regimen without ribavirin. In the genotype 1b study, the SVR12 rates were 99.5% (95% CI, 98.6 to 100.0) in patients who received the regimen with ribavirin and 99.0% (95% CI, 97.7 to 100.0) in patients who received the regimen without ribavirin. Secondary: In the genotype 1a study, the SVR rates among patients who received ribavirin and those who did not were both noninferior and superior to the historical rate with telaprevir and PEG/RBV in treatment-naïve adults with HCV genotype 1a infection and no cirrhosis. The regimen without ribavirin did not meet the noninferiority criterion as compared with the regimen with ribavirin, because the lower boundary of the CI for the difference (-6.8%; 95% CI, -12.0 to -1.5)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 12 weeks and dasabuvir 250 mg twice daily for 12 weeks and placebo (ABT-450 is the experimental name for paritaprevir)	10,000 IU/mL		receive ribavirin, hemoglobin level below the lower limit of the normal range at the end of treatment, and the percentage of patients in each group with virologic failure during treatment or relapse after treatment	crossed the noninferiority margin of 10.5%. In addition, the upper boundary of the confidence interval did not cross zero, indicating a significant difference between groups. In the genotype 1b study, the SVR rates among patients who received ribavirin and those who did not were both noninferior and superior to the historical rate with telaprevir and PEG/RBV among previously untreated adults with HCV genotype 1b infection and no cirrhosis. In addition, the SVR rate among patients who did not receive ribavirin was noninferior to the rate among those who received ribavirin (difference, -0.5%; 95% CI, -2.1 to 1.1). Among the patients in the genotype 1a study who had a hemoglobin level within the normal range at baseline, 42.0% of patients who received the antiviral regimen with ribavirin and 3.9% of patients who received the ribavirin-free regimen had a hemoglobin level below the lower limit of the normal range at the end of treatment (P<0.001). Similarly, in the genotype 1b study, 51.2% of patients who received ribavirin had a low hemoglobin level at the end of treatment, as compared with 3.4% of patients who did not receive ribavirin (P<0.001). Among patients with genotype 1a infection, the rate of virologic failure was higher in the ribavirin-free group than in the group receiving ribavirin (7.8 vs 2.0%). Of patients with genotype 1b infection, none had virologic failure in the ribavirin-free group and one had virologic failure (0.48%) in the group receiving ribavirin.
Poordad et al.[26] (2014) TURQUOISE-II ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 12 weeks and	MC, OL, R Patients 18 to 70 years of age with chronic HCV genotype 1 infection, treatment-naïve or previously treated with	N=380 12 to 24 weeks	Primary: SVR12 compared to historical control Secondary: SVR12 with 12- vs 24-week	Primary: The SVR12 rates were 91.8% (97.5% CI, 87.6 to 96.1) in the 12-week group and 95.9% (97.5% CI, 92.6 to 99.3) in the 24-week group. These rates were statistically noninferior and superior to the historical control rate with telaprevir and PEG/RBV among patients with HCV genotype 1 infection and cirrhosis (47%; 95% CI, 41 to 54). Secondary: The difference in the SVR12 rates between the 12- and 24-week

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dasabuvir 250 mg twice daily for 12 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 12 weeks vs ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 24 weeks and dasabuvir 250 mg twice daily for 24 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 24 weeks (ABT-450 is the experimental name for paritaprevir)	PEG/RBV, documented cirrhosis by means of liver biopsy, Child–Pugh class A score <7, no current or past clinical evidence of Child–Pugh class B or C, HCV RNA >10,000 IU/mL, platelets ≥60,000/mm^3, serum albumin ≥2.8 g/dL, total bilirubin <3 mg/dL, INR≤2.3, and serum alpha-fetoprotein ≤100 ng/mL		treatment, virologic failure during treatment or relapse after treatment	treatment groups was not significant (P=0.09). The SVR rates with 12- vs 24-week treatment were 88.6 vs 94.2% in genotype 1a patients; 98.5 vs 100% in genotype 1b patients; 94.2 vs 94.6% in treatment-naïve patients; 96.6 vs 100% in relapsers with prior PEG/RBV; 94.4 vs 100% in prior partial responders to PEG/RBV; and 86.7 vs 95.2% in prior null responders to PEG/RBV. Among patients with HCV genotype 1a infection and a prior null response to PEG/RBV, SVR was achieved in 92.9% (95% CI, 85.1 to 100) in the 24-week group as compared to 80.0% (95% CI, 68.9 to 91.1) in the 12-week group. Virologic failure during treatment or relapse after treatment occurred in 6.2% and 2.3% of patients in the 12-week and 24-week groups, respectively. Virologic failure during treatment occurred 0.5% (95% CI, 0 to 1.4) and 1.7% (95% CI, 0 to 3.7) of patients in the 12-week and 24-week groups, respectively. Significantly more patients in the 12-week group than in the 24-week group had a relapse: 5.9% (95% CI, 2.7 to 9.2) vs 0.6% (95% CI, 0 to 1.8).
Jacobson et al.[27] (2014) QUEST-1 Simeprevir 150 mg once daily plus peginterferon alfa-2a plus ribavirin for 12 weeks, followed	DB, MC, PC, RCT Patients (aged ≥18 years) with chronic HCV genotype 1	N=394 72 weeks	Primary: SVR12 Secondary: SVR24, rapid virological response	Primary: SVR12 was achieved in a higher percentage of patients in the simeprevir group than in the placebo group (80 vs 50%), and the difference stratified by HCV genotype 1 subtype and IL28B genotype was significant (29.3%; 95% CI, 20.1 to 38.6; P<0.0001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
by peginterferon alfa-2a plus ribavirin (simeprevir group) vs placebo plus peginterferon alfa-2a plus ribavirin for 12 weeks, followed by peginterferon alfa-2a plus ribavirin (placebo group)	infection and no history of HCV treatment		(RVR), adverse effects	RVR was higher in the simeprevir group than in the placebo group (80 vs 12%). In the simeprevir group, 181 (90%) of 202 patients with RVR achieved SVR12. A higher proportion of patients in the simeprevir group had SVR24 than in the placebo group (83 vs 60%; weighted difference 18.1%; 95% CI, –0.4 to 36.6; P=0.0253). Overall frequencies of adverse events were similar in the two groups during the first 12 weeks of treatment and for the entire treatment. The adverse events resulted in less than 1% of patients permanently discontinuing simeprevir or placebo in the first 12 weeks and during the entire treatment period. In the first 12 weeks, 3% of patients in the simeprevir group discontinued all study drugs compared with 2% in the placebo group.
Manns et al.[28] (2014) QUEST-2 Simeprevir 150 mg once daily plus peginterferon alfa-2a or 2b plus ribavirin for 12 weeks, followed by peginterferon alfa-2a or 2b plus ribavirin (simeprevir group) vs placebo plus peginterferon alfa-2a or 2b plus ribavirin for 12 weeks, followed by peginterferon alfa-2a or 2b plus ribavirin (placebo group)	DB, MC, PC, PG, RCT Patients (aged ≥18 years) with chronic HCV genotype 1 infection and no history of HCV treatment	N=391 72 weeks	Primary: SVR12 Secondary: Rapid virological response (RVR), activity, safety, and tolerability of simeprevir in the two subpopulati-ons of patients who were given peginterferon alfa 2a or 2b, adverse events	Primary: Significantly more patients achieved SVR12 in the simeprevir group than in the placebo group (209 [81%] of 257 vs 67 [50%] of 134). The adjusted difference weighted by HCV subtype, IL28B genotype, and peginterferon type as stratification factors was 32.2% (95% CI, 23.3 to 41.2; P<0.0001). Secondary: A significantly higher percentage of patients achieved SVR12 in the simeprevir group than in the placebo group, irrespective of the type of peginterferon they were given: 68 (88%) of 77 patients in the simeprevir group randomly assigned to peginterferon alfa-2a achieved SVR12 compared with 28 (62%) of 45 in the placebo group difference 33.9%; 95% CI, 21.0 to 46.8; P<0.0001). Of the patients randomly assigned to peginterferon alfa-2b, 62 (78%) of 80 patients in the simeprevir group versus 18 (42%) of 43 in the placebo group achieved SVR12 (46.1%; 33.9 to 58.3; P<0.0001). Overall, the proportions of patients who had adverse events in the first 12 weeks of treatment were similar in the simeprevir and placebo groups, and the proportions were similar in the two groups for the entire treatment.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fried et al.[29] (2013) PILLAR Simeprevir at doses of either 75 or 150 mg administered orally once daily for 12 or 24 weeks in combination with pegylated interferon (Peg-IFN) α-2a 180 µg/week and ribavirin (RBV) 1,000 to 1,200 mg/day vs Placebo in combination with Peg-IFN α-2a 180 µg/week and RBV 1,000 to 1,200 mg/day Participants who were randomized to 12 weeks of simeprevir therapy received an additional 12 weeks of placebo plus Peg-IFN and RBV.	DB, PC, RCT Adult patients with chronic hepatitis C with plasma HCV RNA >100,000 IU/mL, infection with HCV genotype 1, never received Peg-IFN, RBV, or other approved or investigational agents for chronic HCV infection	N=386 48 weeks (plus 24 weeks of follow up)	Primary: proportion of patients with HCV RNA <25 IU/mL undetectable at week 72 Secondary: SVR12, SVR24, adverse events	Primary: SVR at week 72 ranged between 70.7 and 84.8% for simeprevir regimens, compared with 64.9% of those treated with Peg-IFN and RBV alone. The differences between simeprevir 150 mg groups and placebo control were statistically significant (P<0.05). Secondary: SVR24 was achieved in 74.7 to 86.1% of those treated with simeprevir regimens, compared to 64.9% of those treated with placebo. All SVR24 comparisons between simeprevir treatment groups and placebo controls were statistically significant (P<0.05 or 0.005), except for simeprevir 75 mg for 24 weeks. The most frequent adverse events (fatigue, influenza-like illness, pruritus, headache, and nausea) were those typically associated with Peg-IFN and RBV therapy and were similar across simeprevir and placebo treatment groups.
Kowdley et al.[30] (2013) ATOMIC Cohort A: sofosbuvir 400 mg orally once daily, peginterferon 180 µg subcutaneously once a week, and ribavirin orally as a divided weight-based daily dose (<75 kg received 1000 mg and those ≥75 kg received 1200 mg) for 12 weeks vs	MC, OL, R Patients with chronic HCV infection (genotypes 1, 4, 5, or 6), aged 18 years or older, and had not previously received treatment for HCV infection	N=316 12 to 24 weeks (plus 24 weeks of follow up)	Primary: SVR24 Secondary: Safety	Primary: Cohort A: 46 of 52 (89%; 95% CI, 77 to 96%) Cohort B: 97 of 109 (89%; 95% CI, 82 to 94%) Cohort C: 135 of 155 (87%; 95% CI, 81 to 92%) No difference was found in the proportions of patients achieving SVR24 between cohorts A and B (P=0.94) or between cohorts A and C (P=0.78), suggesting no additional benefit of treatment durations longer than 12 weeks. Secondary: Most patients (97 to 99%) had at least one adverse event during the study. The most common adverse events were those consistent with the known safety profile for peginterferon and ribavirin: fatigue, headache, and nausea.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cohort B received the same drugs at the same doses for 24 weeks vs Cohort C received the same regimen as individuals in cohort A followed by an additional 12 weeks of sofosbuvir monotherapy for half the patients, or sofosbuvir plus ribavirin for the other half (with patients randomly allocated to these subcohorts)				
Lawitz et al.[31] (2013) NEUTRINO and FISSION NEUTRINO: Sofosbuvir 400 mg once daily for 12 weeks, peginterferon alfa-2a 180 µg once weekly for 12 weeks, and ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) for 12 weeks FISSION: Sofosbuvir 400 mg once daily for 12 weeks and ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) for 12 weeks vs peginterferon alfa-2a 180 µg once	NEUTRINO: MC, OL, SG Patients ≥18 years of age with confirmed diagnosis of chronic HCV infection (genotypes 1, 4, 5, or 6), serum HCV RNA levels of ≥10,000 IU/mL during screening, and who had never received treatment for HCV infection FISSION:	NEUTRINO: N=327 12 weeks FISSION: N=499 24 weeks	NEUTRINO: Primary: SVR12 Secondary: Not reported FISSION: Primary: SVR12 Secondary: Not reported	NEUTRINO: Primary: Treatment with sofosbuvir added to peginterferon alfa-2a and ribavirin achieved a SVR12 in 90% of patients (95% CI, 87 to 93). In addition, this regimen was found to be more effective in achieving a SVR12 compared to an adjusted historical response rate of 60% (P<0.001) observed in studies of telaprevir and boceprevir. The rate of SVR12 was 92% (95% CI, 89 to 95) among patients without cirrhosis and 80% (95% CI, 67 to 89) among those with cirrhosis. A SVR12 occurred in 98% of patients with the CC genotype of IL28B, as compared to 87% of patients with the non–CC IL28B genotype. Rates of SVR12 were similar among various HCV genotypes: 89% for patients with genotype 1 (92% for genotype 1a and 82% for genotype 1b) and 96% for those with genotype 4. The single patients with genotype 5 and all six patients with genotype 6 achieved SVR12. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
weekly for 24 weeks and ribavirin 800 mg/day in two divided doses for 24 weeks	AC, MC, OL, R Patients ≥18 years of age with confirmed diagnosis of chronic HCV infection (genotypes 2 or 3), serum HCV RNA levels of ≥10,000 IU/mL during screening, and who had never received treatment for HCV infection			FISSION: Primary: A SVR12 was achieved in 67% of patients in both sofosbuvir plus ribavirin group and peginterferon alfa-2a plus ribavirin group. Response rates in patients receiving sofosbuvir plus ribavirin were lower among patients with genotype 3 infection than among those with genotype 2 infection (56 vs 97%). Among patients with cirrhosis at baseline, 47% of patients receiving sofosbuvir plus ribavirin had a SVR12 compared to 38% of those receiving peginterferon alfa-2a plus ribavirin. Secondary: Not reported
Lawitz et al.[32] (2013) Cohort A (HCV genotype 1 patients): sofosbuvir 200 mg, sofosbuvir 400 mg, or placebo (randomized 2:2:1) for 12 weeks in combination with peginterferon (180 µg per week) and ribavirin (1000 to 1200 mg daily), followed by peginterferon and ribavirin for an additional 12 weeks or 36 weeks (depending on viral response) Cohort B (genotypes 2 or 3): open-label sofosbuvir 400 mg plus peginterferon and ribavirin for 12 weeks	DB, RCT Treatment-naive patients aged 18 to 70 with HCV genotypes 1, 2, and 3 and no cirrhosis	N=122 (Cohort A) N=25 (Cohort B)	Primary: Safety and tolerability Secondary: SVR12, SVR24	Primary: The most common adverse events during sofosbuvir dosing (up to week 12) were fatigue, headache, nausea, chills, pain, and insomnia. Most adverse events were mild or moderate in severity. Eight patients in cohort A discontinued treatment because of an adverse event, six within the first 12 weeks of treatment (three in the placebo group and three in the 400 mg sofosbuvir group). Secondary: In cohort A, compared with the placebo group, SVR12 and SVR24 were more common in the 200 mg sofosbuvir group (differences of 30%; 95% CI, 12 to 49; P=0.001, and 28%, nine to 46; P=0.0017, respectively) and in the 400 mg sofosbuvir group (differences of 32%; 13 to 51; P=0.0005, and 30%, 11 to 49; P=0.0006, respectively). Of the 25 patients in cohort B, most achieved both SVR12 and SVR24 (23 patients (92%) for both SVR12 and 24; 95% CI, 74 to 99).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Curry et al.[33] (2015) ASTRAL-4 Sofosbuvir 400 mg/ velpatasvir 100 mg once daily for 12 weeks vs sofosbuvir 400 mg/ velpatasvir 100 mg once daily for 12 weeks and ribavirin (1,000 mg/day if weight <75 kg or 1,200 mg/day if weight ≥75 kg) twice daily for 12 weeks vs sofosbuvir 400 mg/ velpatasvir 100 mg once daily for 24 weeks	MC, OL, R Patients >18 years of age with chronic HCV infection of any genotype and decompensated cirrhosis classified as CTP class B (score of 7 to 9)	N=267 12 to 24 weeks	Primary: SVR12‡ Secondary: Change from baseline in the CTP and MELD scores at 12 weeks after the end of treatment	Primary: Overall SVR12 rates were 83% (75/90; 95% CI, 74 to 90), 94% (82/87; 95% CI, 87 to 98), and 86% (77/90; 95% CI, 77 to 92) among patients who received sofosbuvir/velpatasvir for 12 weeks, sofosbuvir/velpatasvir and ribavirin, and sofosbuvir/velpatasvir for 24 weeks, respectively. All three treatment groups met the prespecified primary efficacy end point of SVR rates exceeding assumed spontaneous rate of HCV clearance of 1% at 12 weeks after treatment (P<0.001 for all three comparisons). Among patients with HCV genotype 1, SVR12 rate was 88% (60/68) for those who received sofosbuvir/velpatasvir for 12 weeks, 96% (65/68) for those who received sofosbuvir/velpatasvir and ribavirin, and 92% (65/71) for those who received sofosbuvir/velpatasvir for 24 weeks. Among patients with HCV genotype 3, SVR12 rate was 85% (11/13) for those who received sofosbuvir/velpatasvir and ribavirin as compared with 50% (7/14) and 50% (6/12) for those who received sofosbuvir/velpatasvir alone for 12 weeks and 24 weeks, respectively. All patients with HCV genotype 2, 4, or 6 achieved SVR12 except for one patient with HCV genotype 2 who died of liver failure after completing 28 days of 24-week sofosbuvir/velpatasvir treatment. Secondary: Of the 250 patients with CTP and MELD scores available at post-treatment week 12, 117 (47%) had an improvement in the CTP score over baseline, 106 (42%) had no change in the CTP score, and 27 (11%) had a worsening in the CTP score. Of the 223 patients with a baseline MELD score of less than 15 for whom MELD data were available at post-treatment week 12, 114 (51%) had an improved MELD score, 49 (22%) had no change in the MELD score, and 60 (27%) had a worsening in the MELD score. Of the 27 patients with a baseline MELD score of 15 or more, 22 (81%)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				had an improved MELD score, three (11%) had no change in the MELD score, and two (7%) had a worsening in the MELD score.
Treatment of chronic hepatitis C: Treatment-experienced patients				
Bacon et al.[34] (2011) RESPOND-2 Group 1 (control): Peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 44 weeks vs Group 2 (response-guided therapy): boceprevir 800 mg three times a day plus peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 32 weeks, followed by an additional 12 weeks of peginterferon alfa-2b plus ribavirin in detectable HCV RNA levels at week 8 but undetectable at week 12 vs Group 3 (fixed duration therapy): boceprevir 800 mg three times a day plus peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 44 weeks All patients entered a 4 week lead in period in which peginterferon alfa-2b and ribavirin were	DB, MC, PC, RCT Previously treated adults with HCV genotype 1 infection with responsiveness to interferon therapy for a minimum of 12 weeks	N=403 48 weeks (plus 24 weeks of follow up)	Primary: SVR, safety Secondary: Proportion of patients with an early response in whom a SVR was achieved, proportion of patients with a relapse	Primary: Rates of SVR were significantly higher with boceprevir-containing regimens compared to control, with overall rates of SVR of 21, 59, and 66% in Groups 1, 2, and 3, respectively (P<0.001). The increase observed with Groups 2 and 3 was largely due to end of treatment rates of response being higher (70 and 77 vs 31%) and relapse rates being lower (15 and 12 vs 32%) compared to Group 1. The absolute difference between Groups 2 and 1 was 34.7 percentage points (95% CI, 25.7 to 49.1), and between Groups 3 and 1 it was 45.2 percentage points (95% CI, 33.7 to 56.8). There was no difference in SVR rates between Groups 2 and 3 (OR, 1.4; 95% CI, 0.9 to 2.2). Overall, the most common adverse events were flulike symptoms, while dysgeusia, rash and dry skin were more commonly reported with boceprevir-containing regimens. A greater proportion of patients receiving boceprevir reported serious adverse events, and there were more discontinuations and dose modifications due to adverse events with boceprevir. Anemia occurred more frequently with boceprevir (43 to 46 vs 20%), and erythropoietin was administered more frequently to patients receiving boceprevir. Secondary: The proportion of patients with an undetectable HCV RNA level at week eight in Groups 2 and 3 (46 and 52%) was approximately six times the proportion in Group 1 (9%). Early response was associated with a high rate of SVR in all three treatment groups (100, 86, and 88% in Groups 1, 2, and 3; P values not reported). The rates of SVR among patients with prior relapse (undetectable HCV RNA level at the end of prior therapy, without subsequent attainment of a SVR) were 29, 69, and 75% in Groups 1, 2, and 3; respectively (P values not reported). And the patients with prior nonresponse (a decrease in the HCV RNA level of ≥2 log10 IU/mL by week 12 of prior therapy but a detectable HCV RNA level

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
administered. Treatment was considered complete in Group 2 if the HCV RNA level was undetectable at weeks 8 and 12 (total duration, 36 weeks). In addition, in all 3 treatment groups, treatment was discontinued for all patients with a detectable HCV RNA level at week 12 based on futility rules; these patients then entered the follow up period.				throughout the course of prior therapy, without subsequent attainment of a SVR), the corresponding rates were 7, 40, and 52% (P values not reported). Virologic breakthrough (achievement of an undetectable HCV RNA level and subsequent occurrence of an HCV RNA level >1,000 IU/mL) and incomplete virologic response (an increase of 1 log10 IU/mL in the HCV RNA level from the nadir, with an HCV RNA level >1,000 IU/mL) were infrequent during the treatment period. Multivariable stepwise logistic-regression analysis served to identify five baseline factor that were significantly associated with achievement of a SVR: assignment to boceprevir (OR for Groups 2 and 3 vs Group 1, 7.3 and 10.7, respectively; P<0.001 for both), previous relapse (OR vs previous nonresponse, 3.1; P<0.001), low viral load at baseline (OR vs high load, 2.5; P=0.02) and absence of cirrhosis (OR vs presence, 2.1; P=0.04).
Flamm et al.[35] (2013) Peginterferon alfa-2a 180 µg weekly plus ribavirin 1,000 or 1,200 mg/day plus placebo for 48 weeks total vs boceprevir 800 mg three times a day plus peginterferon alfa-2a 180 µg weekly plus ribavirin 1,000 or 1,200 mg/day for 44 weeks (total treatment duration of 48 weeks) All patients entered a 4 week lead in period in which peginterferon alfa-2a and ribavirin were	PC, PG, RCT Patients with chronic HCV genotype 1 infection who were relapsers or nonresponders to a previous course of peginterferon alfa and ribavirin	N=201 48 weeks (plus 24 weeks of follow up)	Primary: SVR Secondary: Proportion of patients whom a SVR was achieved by prior response (relapse and nonresponse), safety	Primary: Rates of SVR were significantly higher with boceprevir-containing regimens compared to placebo, with overall rates of SVR of 21% in the peginterferon/ribavirin only treatment group compared to and SVR rate of 64% with boceprevir (P<0.001). Secondary: The rates of SVR among patients with prior relapse (undetectable HCV RNA level at the end of prior therapy, without subsequent attainment of a SVR) were 28% in the peginterferon/ribavirin only treatment group compared to and SVR rate of 70% with boceprevir (P values not reported). The rates of SVR among patients with prior nonresponse (a decrease in the HCV RNA level of ≥2 $\log_{10}$ IU/mL by week 12 of prior therapy but a detectable HCV RNA level throughout the course of prior therapy, without subsequent attainment of a SVR), were 5% in the peginterferon/ribavirin only treatment group compared to and SVR rate of 47% with boceprevir (P values not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
administered. In addition, in all treatment groups, treatment was discontinued for all patients with a detectable HCV RNA level at week 12 based on futility rules; these patients then entered the follow up period.				Overall, the most common adverse events were flulike symptoms, while dysgeusia, diarrhea, rash, myalgia, leukopenia and vomiting were more commonly reported with boceprevir-containing regimens. A greater proportion of patients receiving boceprevir reported serious adverse events (13 vs 10%), and there were more discontinuations (17 vs 3%) and dose modifications (43 vs 22%) due to adverse events with boceprevir. Anemia occurred more frequently with boceprevir (50 vs 57%). Anemia was managed with dose reduction in 8% of control group and 0% in the boceprevir group. Erythropoietin was administered more frequently to patients receiving boceprevir (28 vs 29%) and a combination of both interventions in 56% of the placebo group and 57% of the boceprevir group). Neutropenia occurred more frequently with boceprevir (31 vs 18%), and granulocyte colony-stimulating factor administered more frequently with boceprevir (14 vs 12%). Secondary: Not reported
Forns et al.[36] (2015) C-SALVAGE Elbasvir/grazoprevir 100 mg/50 mg once daily for 12 weeks and ribavirin twice daily (total daily dose of 800 mg to 1,400 mg based on weight) for 12 weeks	OL Patients ≥18 years of age with chronic HCV genotype 1 coinfection with HCV RNA ≥10,000 IU/mL who previously failed ≥4 weeks of peginterferon and ribavirin combined with boceprevir,	N=79 12 weeks	Primary: SVR12 Secondary: Not reported	Primary: All participants received an HCV protease inhibitor; none had taken sofosbuvir. Of the 79 patients treated with ≥1 dose of study drug, 66 (84%) had a history of virologic failure on a regimen containing a NS3/4A protease inhibitor; 12 others discontinued prior treatment because of adverse effects. SVR12 rates were 96.2% (76/79) overall, including 93.3% (28/30) in patients with genotype 1a infection, 95.5% (63/66) in patients with prior virologic failure, 100% (43/43) in patients without baseline RAVs, 91.2% (31/34) in patients with baseline NS3 RAVs, 75.0% (6/8) of patients with baseline NS5A RAVs, and 66.7% (4/6) of patients with both baseline NS3 and NS5A RAVs, and 94.1% (32/34) in cirrhotic patients. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	telaprevir, simeprevir, or sofosbuvir			
Buti et al.[37] (2016) C-SALVAGE Elbasvir/grazoprevir 100 mg/50 mg once daily for 12 weeks and ribavirin twice daily (total daily dose of 800 mg to 1,400 mg based on weight) for 12 weeks	OL Patients ≥18 years of age with chronic HCV genotype 1 coinfection with HCV RNA ≥10,000 IU/mL who previously failed ≥4 weeks of peginterferon and ribavirin combined with boceprevir, telaprevir, or simeprevir	N=79 24 weeks	Primary: Not reported Secondary: SVR24	Primary: Not reported Secondary: The SVR24 rate was 96.2% (76/79) overall, with all three relapses occurring by post-therapy week eight. Every NS3 and NS5A variant detected at baseline reappeared at the time of relapse and persisted throughout the available follow-up period. NS3_A156T emerged in virus from each patient at relapse, but rapidly disappeared over the ensuing two weeks in two patients. NS5A_Y93H emerged in virus from two patients at relapse and persisted for the entire follow-up period.
Poodard et al.[38] MAGELLAN-1 Part 1 (2017) Glecaprevir 200 mg and pibrentasvir 80 mg once daily for 12 weeks (Group A) vs glecaprevir 300 mg plus pibrentasvir 120 mg and ribavirin 800 mg once daily for 12 weeks (Group B)	MC, OL, RCT Patients 18 to 70 years of age with chronic HCV genotype 1 without cirrhosis who failed prior treatment with a DAA	N=50 12 weeks	Primary: SVR12 Secondary: Not reported	Primary: The SVR12 rates were 100% (6/6; 95% CI, 61 to 100), 95% (21/22; 95% CI, 78 to 99), and 86% (19/22; 95% CI, 67 to 95) in Groups A, B, and C, respectively. Virologic failure occurred in one patient in both Group B and C; two patients were lost to follow-up in Group C. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs glecaprevir 200 mg plus pibrentasvir 120 mg once daily for 12 weeks (Group C)				
Afdhal et al.[39] (2014) ION 2 Ledipasvir 90 mg and sofosbuvir 400 mg once daily for 12 weeks vs ledipasvir 90 mg and sofosbuvir 400 mg once daily for 12 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 12 weeks vs ledipasvir 90 mg and sofosbuvir 400 mg once daily for 24 weeks vs ledipasvir 90 mg and sofosbuvir 400 mg once daily for 24 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75	MC, OL, R Patients ≥18 years of age with chronic HCV genotype 1 infection who had not had a SVR with either PEG/ribavirin or NS3/4A protease inhibitor combined with PEG/ribavirin	N=440 12 to 24 weeks	Primary: SVR12 Secondary: SVR24	Primary: In all four treatment groups, the SVR12 rate was higher than the adjusted historical response rate of 25% (P<0.001 for all comparisons). The SVR12 rates was 94% (95% CI, 87 to 97) in the group that received 12 weeks of ledipasvir/sofosbuvir; 96% (95% CI, 91 to 99) in the group that received 12 weeks of ledipasvir/sofosbuvir with ribavirin; 99% (95% CI, 95 to 100) in the group that received 24 weeks of ledipasvir/sofosbuvir; and 99% (95% CI, 95 to 100) in the group that received 24 weeks of ledipasvir/sofosbuvir with ribavirin. Among patients with cirrhosis who were assigned to 12 weeks of treatment, the SVR12 rates were 86% for those who received ledipasvir/sofosbuvir and 82% for those who received ledipasvir/sofosbuvir with ribavirin; the respective rates among patients without cirrhosis were 95% and 100%. Among patients with cirrhosis who were assigned to 24 weeks of treatment, the SVR12 rates were 100% for those who received ledipasvir/sofosbuvir and 100% for those who received ledipasvir/sofosbuvir with ribavirin; the respective rates among patients without cirrhosis were 99% and 99%. The difference between the SVR rates among patients with cirrhosis who received 12 weeks of treatment and the SVR among patients with cirrhosis who received 24 weeks of treatment was statistically significant (P=0.007). Secondary: All patients who had a SVR12 also had a SVR24. No patient had a relapse after post-treatment week 12.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
kg) in two divided doses for 24 weeks				
Bourlière et al.[40] (2015) SIRIUS Ledipasvir 90 mg and sofosbuvir 400 mg in a fixed-dose combination tablet plus placebo for 12 weeks, followed by ledipasvir-sofosbuvir once daily plus ribavirin given in a divided daily dose for 12 weeks vs once daily ledipasvir-sofosbuvir 90-400 mg plus placebo for 24 weeks	DB, MC, RCT Patients with HCV genotype 1 and compensated cirrhosis who had not achieved SVR after successive treatments with pegylated interferon and protease-inhibitor regimens	N=155 24 weeks	Primary: SVR12 Secondary: SVR12 rates between the two treatment groups by randomization stratification factors	Primary: SVR12 rates were 96% (95% CI, 89 to 99) in the ledipasvir-sofosbuvir plus ribavirin group and 97% (91 to 100) in the ledipasvir-sofosbuvir group (P=0.63). Secondary: SVR12 rates when compared with previous treatment response were 97% in ledipasvir-sofosbuvir plus ribavirin group and 94% in the ledipasvir-sofosbuvir group in patients who had never achieved undetectable HCV RNA, vs 96% and 100%, respectively, in patients who had previously achieved undetectable HCV RNA.
Zeuzem et al.[41] (2014) SAPPHIRE-II ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 12 weeks and dasabuvir 250 mg twice daily for 12 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 12	DB, MC, PC, R Patients 18 to 70 years of age with chronic HCV genotype 1 infection without cirrhosis, relapsers or nonresponders with prior PEG/RBV treatment, and HCV RNA >10,000 IU/mL	N=394 12 weeks	Primary: SVR12 compared to historical control Secondary: Normalization of the alanine aminotransferase level, SVR by HCV genotype (1a or 1b), virologic failure during treatment, and post-treatment	Primary: Treatment with the active-regimen lead to a SVR12 of 96.3% (95% CI, 94.2 to 98.4) which was noninferior and superior to the historical control SVR rate of 65% (95% CI, 60 to 70) among previously treated patients with HCV genotype 1 infection and no cirrhosis who had received retreatment with telaprevir and PEG/RBV (P value not reported). Secondary: The rate of normalization of the alanine aminotransferase level was significantly higher in the active-regimen group than in the placebo group (96.9 vs 12.8%, P<0.001). The SVR rates were similar between patients with HCV genotype 1a infection (96.0%; 95% CI, 93.0 to 98.9) and those with HCV genotype 1b infection (96.7%; 95% CI, 93.6 to 99.9). The HCV genotype (1a or 1b) could not be determined for one patient, who had a SVR12.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
weeks vs placebo (ABT-450 is the experimental name for paritaprevir)			relapse	No patient had virologic failure during treatment. Of the 293 patients who completed therapy, 2.4% had a post-treatment viral relapse.
Andreone et al.[42] (2014) PEARL-II ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 12 weeks and dasabuvir 250 mg twice daily for 12 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 12 weeks vs ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 12 weeks and dasabuvir 250 mg twice daily for	MC, OL, R Patients 18 to 70 years of age with chronic HCV genotype 1b infection for at least six months, and HCV RNA >10,000 IU/mL, no cirrhosis, and prior failure of therapy with PEG/RBV	N=179 12 weeks	Primary: SVR12 compared to historical control Secondary: Proportion of patients with decreased hemoglobin level to less than the lower limit of normal at the end of treatment, superiority of both groups to historical SVR rate, noninferiority of both treatment groups, virologic failure during treatment, and post-treatment	Primary: The SVR12 rate was 96.6% (95% CI, 92.8 to 100) in the group receiving ribavirin and 100% (95% CI, 95.9 to 100) in the group not being treated with ribavirin. These rates were statistically noninferior to the historical SVR rate for telaprevir and PEG/RBV in comparable treatment-experienced patients. Secondary: Hemoglobin levels less than the lower limit of normal at the end of treatment were more common in patients receiving ribavirin compared to those that did not (42.0 vs 5.5%, respectively; P<0.001), although clinically significant grade 2 hemoglobin level declines to <10 g/dL at the end of treatment occurred in only two patients (1.1%), both in the group receiving ribavirin. The SVR12 rates in the group receiving ribavirin (96.6%) and in the group not being treated with ribavirin (100%) were statistically superior to the historical SVR rate for telaprevir and PEG/RBV in comparable treatment-experienced patients. The SVR12 rates in the group not receiving ribavirin were noninferior to those in the group receiving ribavirin (difference, 3.4%; 95% CI, -0.4 to 7.2) No patients from either treatment group experienced on-treatment virologic failure or post-treatment relapse. Of the three patients in the group receiving ribavirin who did not achieve SVR12, there were two patients (2.3%) who discontinued study drug.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
12 weeks (ABT-450 is the experimental name for paritaprevir)			relapse	
Forns et al.[43] (2014) Simeprevir 150 mg once daily plus peginterferon alfa-2a 180 µg weekly plus ribavirin 1,000 or 1,200 mg/day depending on body weight, respectively (PR) for 12 weeks followed by response-guided treatment with PR alone for 12 or 36 weeks vs placebo with PR for 12 weeks followed by PR alone for 36 weeks	DB, MC, PC, PG, RCT Adults >18 years with confirmed genotype 1 HCV infection and screening plasma HCV-RNA levels >10,000 IU/mL, who had relapsed after 24 weeks or more of interferon-based therapy (undetectable HCV-RNA at end of treatment [EOT] or within 2 months after EOT, with documented relapse within 1 year after therapy).	N=393 24 or 48 weeks (plus 72 weeks of follow up)	Primary: SVR12 rates Secondary: SVR24, rapid virologic response (RVR) rate, viral breakthrough, on-treatment failure, viral relapse, adverse events	Primary: In the simeprevir/PR arm, an SVR12 rate of 79.2% (206 of 260) was observed compared with 36.1% (48 of 133) with placebo/PR. The difference between the two groups (controlling for HCV 1 subtype and IL28B genotype as stratification factors) was statistically significant at 43.8% (95% CI, 34.6 to 53.0; P<0.001). Secondary: The RVR rate was 77.2% (200 of 259) in the simeprevir/PR group compared with 3.1% (four of 129) treated with placebo/PR. Among simeprevir-treated patients who achieved RVR, 86.5% (173 of 200) subsequently achieved SVR12. The rate of on-treatment failure was 3.1% (eight of 260) for simeprevir/PR and 27.1% (36 of 133) for placebo/PR. During the first 12 weeks of treatment, the most frequent adverse events in the simeprevir/PR group (>25% of patients) were headache, fatigue, and influenza-like illness. Rash, pruritus, neutropenia, and anemia were comparable between the simeprevir and placebo groups. No patient discontinued simeprevir or placebo alone owing to adverse events.
Zeuzem et al.[44] (2014) ASPIRE	DB, MC, PC, RCT Adults aged 18	N=462 48 weeks (plus 72	Primary: SVR24 Secondary:	Primary: In the overall population, SVR24 was achieved in 60.6 to 80.0% of simeprevir arms and 22.7% of the placebo arm (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Group 1: 12 weeks of simeprevir 100 mg plus peginterferon alfa-2a (PegIFN)/ ribavirin (RBV), followed by 36 weeks of PegIFN/RBV group 2: 12 weeks of simeprevir 150 mg plus PegIFN/RBV, followed by 36 weeks of PegIFN/RBV group 3: 24 weeks of simeprevir 100 mg plus PegIFN/RBV, followed by 24 weeks of PegIFN/RBV group 4: 24 weeks of simeprevir 150 mg plus PegIFN/RBV, followed by 24 weeks of PegIFN/RBV group 5: 48 weeks of simeprevir 100 mg plus PegIFN/RBV group 6: 48 weeks of simeprevir 150 mg plus PegIFN/RBV group 7 (placebo control group): 48 weeks of simeprevir-matched placebo plus PegIFN/RBV In all simeprevir treatment arms, when patients were not receiving simeprevir, they received a matched placebo	to 70 years, chronically infected with HCV genotype 1 and with plasma HCV RNA >10,000 IU/mL at screening were included in the study. All patients must have received at least one prior course of PegIFN/RBV for >12 consecutive weeks and not discontinued therapy due to tolerability	weeks of follow up)	Rapid virologic Response, SVR12, adverse effects	When pooling dosage dosages, SVR24 was achieved by 129 of 197 patients (65.5%; range, 60.6 to 69.7%) of the simeprevir 100 mg group and 145 of 199 patients (72.9%; range, 66.7 to 80.0%) of the simeprevir 150 mg group, compared with 15 of 66 patients (22.7%) on placebo (P<0.001 for both comparisons). Pooling treatment duration, SVR24 was achieved by 90 of 132 patients (68.2%; range, 66.7 to 69.7%) on simeprevir for 12 weeks, 92 of 133 (69.2%; range, 66.2 to 72.1%) of those on simeprevir for 24 weeks, and in 92 of 131 (70.2%; range, 0.6 to 80.0%) of those on simeprevir for 48 weeks. Secondary: The proportions of patients achieving SVR12 (60.6 to 80.0% of simeprevir- and 23% of placebo-treated patients) were very similar to the proportions achieving SVR24. The most frequently reported adverse events (>25% of patients) with simeprevir plus PegIFN/RBV were fatigue, headache, pruritus, influenza-like illness, and neutropenia. No major difference was reported with respect to the incidence of serious adverse events, occurring in 7.8% (N=31) and 6.1% (N=4) of patients treated with simeprevir and placebo, respectively.
Bourlière et al.[45] (2017)	**POLARIS-1** DB (genotype 1	**POLARIS-1** N=415	Primary: SVR12	Primary: **POLARIS-1**

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
POLARIS-1 and POLARIS-4 **POLARIS-1** Sofosbuvir 400 mg/velpatasvir 100 mg/voxilaprevir 100 mg once daily for 12 weeks vs placebo **POLARIS-4** Sofosbuvir 400 mg/velpatasvir 100 mg/voxilaprevir 100 mg once daily for 12 weeks vs sofosbuvir 400 mg/velpatasvir 100 mg once daily for 12 weeks	only), MC, PC (genotype 1 only), RCT (genotype 1 only) **POLARIS-4** AC, OL, MC, RCT (genotype 1, 2, and 3 only) Patients >18 years of age with chronic HCV genotype 1 through 6 infection (POLARIS-1) or HCV genotype 1 through 4 infection (POLARIS-4) who were previously treated with a regimen containing an NS5A inhibitor (POLARIS-1) or with any DAA regimen except an NS5A inhibitor or protease inhibitor plus	12 weeks **POLARIS-4** N=333 12 weeks	Secondary: SVR4, SVR24, HCV RNA<15 IU/mL during treatment, the change in HCV RNA level from baseline (day 1), virologic failure, and viral resistance	The overall SVR12 rate was 96% (95% CI, 93 to 98) in the sofosbuvir/velpatasvir/voxilaprevir group, which was significantly greater than the prespecified performance goal of 85% (P<0.001). None of the patients who received placebo had a sustained virologic response. In the sofosbuvir/velpatasvir/voxilaprevir group, SVR12 rates were 96% (97/101) in patients with genotype 1a infection, 100% (45/45) with genotype 1b, 100% (5/5) with genotype 2, 95% (74/78) with genotype 3, 91% (20/22) with genotype 4, 100% (1/1) with genotype 5, and 100% (6/6) with genotype 6. The SVR12 rates in patients with and without compensated cirrhosis were 93% and 99%, respectively. **POLARIS-4** The overall SVR12 rate was 98% (95% CI, 95 to 99) in the sofosbuvir/velpatasvir/voxilaprevir group, which was significantly greater than the prespecified performance goal of 85% (P<0.001). The SVR12 rate of 90% (95% CI, 84 to 94) in the sofosbuvir/velpatasvir group was not significantly greater than the prespecified performance goal of 85% (P<0.09). In the sofosbuvir/velpatasvir/voxilaprevir group, SVR12 rates were 98% (53/54) in patients with genotype 1a infection, 96% (23/24) with genotype 1b, 100% (31/31) with genotype 2, 96% (52/54) with genotype 3, and 100% (19/19) with genotype 4. In the sofosbuvir/velpatasvir group, SVR12 rates were 89% (39/44) in patients with genotype 1a infection, 95% (21/22) with genotype 1b, 97% (32/33) with genotype 2, and 85% (44/52) with genotype 3. In patients without cirrhosis, the SVR12 rate was 98% among those receiving sofosbuvir/velpatasvir/voxilaprevir and 94% among those receiving sofosbuvir/velpatasvir, as compared with 98% and 86%, respectively, among patients with cirrhosis.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	peginterferon and ribavirin (POLARIS-4)			Secondary: **POLARIS-1** The SVR4 rate in the sofosbuvir/velpatasvir/voxilaprevir group was 98% (257/263). Of the 253 patients with an SVR12, all 249 patients who returned for the post-treatment week 24 visit achieved SVR24. The proportion of patients with HCV RNA <15 IU/mL in the sofosbuvir/velpatasvir/voxilaprevir group was 57% (149/263) at week 2, 93% (243/262) and week 4, 100% (262/262) at week 8, and 100% (260/261) at week 12 of treatment. The mean changes in HCV RNA (log_{10} IU/mL) from baseline (day 1) in the sofosbuvir/velpatasvir/voxilaprevir group were -4.2 at week 1, -4.81 at week 2, -5.07 at week 4, -5.11 at week 8, and -5.10 at week 12. Of 263 patients who received sofosbuvir/velpatasvir/voxilaprevir, 10 did not achieve an SVR12. Of these 10 patients, seven had virologic failure, including one on-treatment virologic breakthrough and six virologic relapses. Of the three remaining patients, two withdrew consent and one was lost to follow-up. Of 248 patients who received sofosbuvir/velpatasvir/voxilaprevir for whom viral sequence data were available, 205 (83%) had viral resistance to NS3 or NS5A inhibitors at baseline. Of these patients, 97% (199 of 205) had a SVR12, as compared with 98% of patients without baseline resistance. Of six patients with virologic relapse, one patient with HCV genotype 4 infection had development of NS5A Y93H resistance. **POLARIS-4** The SVR4 rates were 98% (179/182) and 91% (138/151) in the in the sofosbuvir/velpatasvir/voxilaprevir and in the sofosbuvir/velpatasvir groups, respectively. Of 177 patients in the sofosbuvir/velpatasvir/voxilaprevir group and 136 patients in the sofosbuvir/velpatasvir group who had SVR12, 173 and 133 patients, respectively, returned for the posttreatment week 24 visit, and all the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				patients achieved SVR24. The proportion of patients with HCV RNA <15 IU/mL in the sofosbuvir/velpatasvir/voxilaprevir group was 63% (114/182) at week 2, 88% (161/182) and week 4, 100% (182/182) at week 8, and 99% (180/182) at week 12 of treatment. The proportion of patients with HCV RNA <15 IU/mL in the sofosbuvir/velpatasvir group was 56% (85/151) at week 2, 91% (137/151) and week 4, 99% (149/151) at week 8, and 99% (149/150) at week 12 of treatment. The mean changes in HCV RNA (log_{10} IU/mL) from baseline (day 1) in the sofosbuvir/velpatasvir/voxilaprevir group were -4.29 at week 1, -4.93 at week 2, -5.13 at week 4, -5.17 at week 8, and -5.17 at week 12. The mean changes in HCV RNA (log_{10} IU/mL) from baseline (day 1) in the sofosbuvir/velpatasvir group were -4.17 at week 1, -4.78 at week 2, -5.06 at week 4, -5.08 at week 8, and -5.09 at week 12. Nineteen patients did not achieve SVR12: four (3%) in the sofosbuvir/velpatasvir/voxilaprevir group and 15 (10%) in the sofosbuvir/velpatasvir group. Of the four patients in the sofosbuvir/velpatasvir/voxilaprevir group who did not achieve SVR12, one (1%) had a virologic relapse by week 4 of follow-up, one died, and two were lost to follow-up. Among the 15 patients in the sofosbuvir/velpatasvir group who did not achieve SVR12, 14 (9%) had a relapse after completing treatment and one (1%) had virologic breakthrough during treatment. Eight of the 14 patients who had a relapse had HCV genotype 3a infection, five had genotype 1a infection, and one had genotype 1b infection. Forty nine percent of enrolled patients had baseline resistance to NS3 or NS5A inhibitors. The SVR12 rates among patients for whom viral sequence data were available and who received sofosbuvir/velpatasvir/ voxilaprevir for 12 weeks was 100% (83/83) among those with baseline resistance and 99% (85/86) among those without baseline resistance, as compared with 90% (63/70) and 89% (67/75), respectively, among those with and those without resistance

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				in the sofosbuvir/velpatasvir group. The single patient in the sofosbuvir/velpatasvir/voxilaprevir group who had a relapse did not have any resistance at either baseline or the time of relapse. Among the 14 patients in the sofosbuvir/velpatasvir group who had a relapse, 11 had resistance, most of which were in the NS5A gene at amino acid position 93.
Treatment of chronic hepatitis C: Treatment-naïve and experienced patients				
Sitole et al.[46] (2013) Triple therapy with boceprevir or placebo, pegylated interferon, and ribavirin vs triple therapy with telaprevir or placebo, pegylated interferon, and ribavirin	MA Treatment-naive and treatment-experienced patients with chronic HCV genotype 1 infection	N=4144 (8 studies) 24 to 48 weeks after completion of treatment	Primary: SVR Secondary: Rate of rapid (at four weeks with telaprevir or eight weeks with boceprevir) viral response, adverse events	Primary: In the treatment-naive patients, SVR at 24 weeks was greater in the telaprevir treated group compared with the control group (OR, 3.31; 95% CI, 2.27 to 4.82; P <0.0001). In the treatment-experienced patients, the SVR rates at 24 weeks were similar between the active and control groups (OR, 4.21; 95% CI, 1.83 to 9.72; P<0.001). In the treatment-naive patients, SVR at 48 weeks was greater in the telaprevir treated group compared with the control group (OR, 1.98; 95% CI, 1.42 to 2.76; P<0.0001). In the treatment-experienced patients, 48-week SVR rates were similar between the triple-therapy and control groups (OR, 8.46; 95% CI, 5.72 to 12.50; P<0.0001). In treatment-naive patients, 24-week SVR was improved in the group that received boceprevir compared with controls (OR, 3.55; 95% CI, 2.66 to 4.56; P<0.0001); this finding was also true in the treatment-experienced subgroup. In the treatment-naive subgroup, 48-week SVR was improved in the group that received boceprevir compared with the control group (OR, 1.98; 95% CI, 1.42 to 2.76); this finding was also true in the treatment-experienced subgroup. An indirect treatment comparison between telaprevir and boceprevir favored telaprevir for inducing 24-week SVR in treatment-naive patients (OR, 1.78; 95% CI, 1.39 to 2.28; P<0.0001); however, the rates of 48-week SVR in treatment-naive patients were similar between telaprevir and boceprevir (OR, 0.82; 95% CI, 0.60 to 1.11; P=0.2). Secondary: Treatment with telaprevir-based triple therapy did not result in more discontinuations due to adverse drug reactions compared with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				controls (OR, 1.43; 95% CI, 0.42 to 4.92; P=0.57). Telaprevir was associated with an increase in treatment-associated adverse events compared with placebo. Boceprevir was associated with increased prevalences of anemia and dysgeusia. Telaprevir and boceprevir were also similar regarding discontinuation from adverse drug reactions (OR, 1.23; 95% CI, 0.95 to 1.60; P=0.11).
Kwo et al.[47] (2014) CORAL-I ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 24 weeks and dasabuvir 250 mg twice daily for 24 weeks and ribavirin (dosing at investigator's discretion) for 24 weeks A stable tacrolimus- or cyclosporine-based immunosuppressive regimen was required, and glucocorticoids were allowed at a dose of ≤5 mg/day. (ABT-450 is the experimental name for paritaprevir)	MC, OL Patients 18 to 70 years of age with chronic HCV genotype 1 infection, HCV RNA >10,000 IU/mL who received a liver transplant ≥12 months before screening because of chronic HCV infection, and Metavir score≤F2 on liver biopsy performed ≤6 months before screening	N=34 24 weeks	Primary: SVR12 Secondary: SVR24, virologic failure during treatment, and post-treatment relapse	Primary: The SVR12 rate was 97% (95% CI, 85 to 100). All five patients infected with genotype 1b (100%) and 28 of 29 patients infected with genotype 1a (97%) had a SVR. Secondary: The SVR24 rate was 97% (95% CI, 85 to 100). All the patients also had HCV RNA <25 IU/mL at the end of treatment. One patient did not have a SVR owing to a relapse on post-treatment day three. No relapses occurred after post-treatment week 12.
Sulkowski et al.[48] (2014)	OL, R	N=211	Primary: SVR12	Primary: In treatment-naïve patients with HCV genotype 2 or 3 infection, the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Group A (genotype 1) Daclatasvir 60 mg once daily for 23 weeks (after seven day lead in with sofosbuvir) and sofosbuvir 400 mg once daily for 24 weeks **Group B (genotype 2 or 3)** Daclatasvir 60 mg once daily for 23 weeks (after seven day lead in with sofosbuvir) and sofosbuvir 400 mg once daily for 24 weeks **Group C (genotype 1)** Daclatasvir 60 mg once daily for 24 weeks and sofosbuvir 400 mg once daily for 24 weeks **Group D (genotype 2 or 3)** Daclatasvir 60 mg once daily for 24 weeks and sofosbuvir 400 mg once daily for	Patients 18 to 70 years of age with HCV RNA >100,000 IU/mL, no evidence of cirrhosis who were treatment-naïve (Groups A through H) or previously failed treatment with boceprevir or telaprevir plus peginterferon alfa and ribavirin (Groups I and J only)	12 or 24 weeks	Secondary: SVR4 and SVR24, safety (adverse events, discontinu-ations due to adverse events, and grade 3 or 4 laboratory abnormalities)	SVR12 rate was 88% (14/16), 93% (13/14), and 86% (12/14) in Groups B, D, F, respectively. The overall SVR12 rate was 89% (39/44) for all three groups. In treatment-naïve patients with HCV genotype 1 infection, the SVR12 rate was 100% (15/15), 100% (14/14), 100% (15/15), 100% (41/41), and 100% (39/41) in Groups A, C, E, G, H, respectively. The overall SVR12 rate was 98% (124/126) for all five groups. In treatment-experienced patients with HCV genotype 1 infection, the SVR12 rate was 100% (21/21) and 95% (19/20) in Groups I and J, respectively. The overall SVR12 rate was 98% (40/41) for the two groups. Secondary: In treatment-naïve patients with HCV genotype 2 or 3 infection, the SVR4 rate was 88% (14/16), 100% (14/14), and 79% (11/14) in Groups B, D, F, respectively. The overall SVR4 rate was 89% (39/44) for all three groups. In treatment-naïve patients with HCV genotype 1 infection, the SVR4 rate was 100% (15/15), 100% (14/14), 100% (15/15), 98% (40/41), and 100% (39/41) in Groups A, C, E, G, H, respectively. The overall SVR4 rate was 98% (123/126) for all five groups. In treatment-experienced patients with HCV genotype 1 infection, the SVR4 rate was 100% (21/21) and 95% (19/20) in Groups I and J, respectively. The overall SVR4 rate was 98% (40/41) for the two groups. In treatment-naïve patients with HCV genotype 2 or 3 infection, the SVR24 rate was 88% (14/16), 100% (14/14), and 93% (13/14) in Groups B, D, F, respectively. The overall SVR24 rate was 93% (41/44) for all three groups. In treatment-naïve patients with HCV genotype 1 infection, the SVR24 rate was 93% (14/15), 100% (14/14), 100% (15/15), 95%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
24 weeks **Group E (genotype 1)** Daclatasvir 60 mg once daily for 24 weeks and sofosbuvir 400 mg once daily for 24 weeks and ribavirin for 24 weeks **Group F (genotype 2 or 3)** Daclatasvir 60 mg once daily for 24 weeks and sofosbuvir 400 mg once daily for 24 weeks and ribavirin for 24 weeks **Group G (genotype 1)** Daclatasvir 60 mg once daily for 12 weeks and sofosbuvir 400 mg once daily for 12 weeks				(39/41), and 93% (38/41) in Groups A, C, E, G, H, respectively. The overall SVR24 rate was 95% (120/126) for all five groups. The most common adverse events were fatigue, headache, and nausea. Two patients discontinued treatment due to adverse events (fibromyalgia in one patient and a stroke in one patient); both had achieved SVR. The most common grade 3 or 4 laboratory abnormalities were low phosphorus and elevated glucose levels.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Group H (genotype 1) Daclatasvir 60 mg once daily for 12 weeks and sofosbuvir 400 mg once daily for 12 weeks and ribavirin for 12 weeks **Group I (genotype 1)** Daclatasvir 60 mg once daily for 24 weeks and sofosbuvir 400 mg once daily for 24 weeks **Group J (genotype 1)** Daclatasvir 60 mg once daily for 24 weeks and sofosbuvir 400 mg once daily for 24 weeks and ribavirin for 24 weeks				
Wyles et al.[49] (2015) ALLY-2	OL, R Patients ≥18	N=203 8 or 12	Primary: SVR12 in treatment-	Primary: The SVR12 rate was 96.4% (80/83) in treatment-naïve patients with HCV genotype 1 infection receiving daclatasvir plus sofosbuvir for

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Daclatasvir 60 mg once daily for eight weeks (treatment-naïve) or 12 weeks (treatment-naïve or treatment-experienced) and sofosbuvir 400 mg once daily for 12 weeks The standard 60 mg dose of daclatasvir was adjusted to 30 mg in patients receiving ritonavir-boosted protease inhibitors and to 90 mg in those receiving efavirenz or nevirapine.	years of age with HIV/HCV coinfection and HCV RNA >10,000 IU/mL Patients previously treated with NS5A inhibitors were excluded.	weeks	naïve patients with HCV genotype 1 infection receiving 12 weeks of treatment Secondary: SVR12 in treatment-naïve patients with HCV genotype 1 infection receiving eight weeks of treatment and treatment-experienced patients with HCV genotype 1 infection receiving 12 weeks of treatment, SVR12 regardless of HCV genotype, virologic response throughout the study, and safety	12 weeks. Secondary: The SVR12 rate was 75.6% (31/41) in treatment-naïve patients with HCV genotype 1 infection receiving daclatasvir plus sofosbuvir for eight weeks. The SVR12 rate was 97.7% (43/44) in treatment-experienced patients with HCV genotype 1 infection receiving daclatasvir plus sofosbuvir for 12 weeks. The SVR12 rates across all HCV genotypes (HCV genotypes 1 through 4) were 97.0% (98/101) in treatment-naïve patients treated for 12 weeks, 76.0% (38/50) in treatment-naïve patients treated for eight weeks, and 98.1% (51/52) in treatment-experienced patients treated for 12 weeks. The decline in HCV RNA levels during the study period was rapid, and 92 to 98% of patients had an HCV RNA <25 IU/mL by week four of treatment. There were no patients with HCV virologic breakthrough during the treatment period. The most common adverse events were fatigue, nausea, and headache. There were no treatment discontinuations due to adverse events. Serious adverse events during treatment included priapism in a patient receiving medication for erectile dysfunction, presyncope plus chest pain, drug abuse plus pulmonary embolism, and syncope plus hypertensive crisis. No serious event was assessed as being related to a study drug by investigators. There were two deaths during post-treatment follow-up, one due to a cardiac arrest and another due to cardiomyopathy of undetermined cause and multiorgan failure. The most common grade 3 or 4 laboratory abnormalities were elevations in the total bilirubin level among patients receiving atazanavir/ritonavir and transient elevations in lipase without associated pancreatitis.
Coilly et al.[50]	OS	N=137	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2016) CUPILT Daclatasvir 60 mg once daily and sofosbuvir 400 mg once daily Use of ribavirin and treatment duration (12 or 24 weeks) at the discretion of each investigator	Patients who have received a liver transplant for an HCV infection, experienced an HCV recurrence whatever the stage of fibrosis, and receiving daclatasvir and sofosbuvir	24 to 36 weeks	SVR12 Secondary: On-treatment (week 4) and end-of-treatment response rates, improvement in liver function	One hundred thirty two out of 137 patients (96.4%) had a SVR at post-treatment week 12. Among the five patients who did not achieve an SVR12, one was lost to follow-up and two died between end-of-treatment and SVR 12. Excluding non-virological failures, the SVR12 rate thus reached 98.5% (132/134). Secondary: By week four of treatment, HCV RNA levels had fallen below the LLOQ in 71 patients (53%). All clinical and biological parameters reflecting liver function and general status improved significantly during treatment.
Nelson DR et al.[51] (2015) ALLY-3 Daclatasvir 60 mg once daily for 12 weeks and sofosbuvir 400 mg once daily for 12 weeks	OL Patients ≥18 years of age (range 24 to 73) with chronic HCV genotype 3 infection who were treatment-naïve or and treatment-experienced (prior interferon alfa with or without ribavirin, sofosbuvir plus ribavirin, or other anti-HCV agents, such as inhibitors of cyclophilin or	N=152 12 weeks	Primary: SVR12 Secondary: Proportion of patients achieving HCV-RNA levels <LLOQ detectable or undetectable, at on-treatment weeks 1, 2, 4, 6, and 8, the end of treatment, and post-treatment weeks 4 and 24; and SVR12 rates by baseline	Primary: The SVR12 was achieved in 90% of treatment-naïve and 86% in treatment-experienced patient, with an overall SVR12 rate of 89%. Secondary: The proportion of patients achieving HCV-RNA levels <LLOQ, detectable or undetectable, at early on-treatment time points in the treatment-naïve and treatment-experienced cohorts, respectively, was 40% and 24% for week one, 77% and 69% for week two, and 94% and 98% for week four. HCV-RNA levels were undetectable at end of treatment in 99% of patients. The SVR12 was 92% (55/60) and 87% (80/92) in patients with CC and non-CC IL28B genotype, respectively. SVR12 rates were higher in patients without cirrhosis (96% [105/109]) than in patients with cirrhosis (63% [20/32]).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	microRNA) with baseline HCV-RNA levels ≥10,000 IU/mL Patients were excluded if they previously received treatment with NS5A inhibitor or discontinued treatment with sofosbuvir plus ribavirin prematurely because of intolerance (other than exacerbation of anemia)		cirrhosis status and IL28B genotype	
Roth et al.[52] (2015) C-SURFER **Immediate-treatment group** Elbasvir/grazoprevir 100 mg/50 mg once daily for 12 weeks vs **Deferred-treatment group** placebo (followed by open-label elbasvir/grazoprevir	DB, MC Patients ≥18 years of age with chronic HCV genotype 1 coinfection, HCV RNA >10,000 IU/mL, treatment-naïve or previously treated with peginterferon alfa plus	**Immediate-treatment group** N=111 **Deferred-treatment group** N=113 **Intensive pharmacokinetic group** N=11	Primary: SVR12 for the combined immediate-treatment group and the pharmacokinetic group with a historical control Secondary: Not reported	Primary: Of the 122 patients in the combined immediate treatment and intensive pharmacokinetic population, six were excluded from analysis for reasons other than virological failure (death, lost to follow-up, noncompliance, patient withdrawal, and withdrawal by physician due to violent behavior). SVR12 in the combined immediate treatment group and intensive pharmacokinetic population was 99.1% (115/116), a higher rate than the historical control rate of 45% (P<0.001) achieved in Taiwanese patients with HCV genotype 1b infection on hemodialysis and receiving peginterferon alfa plus ribavirin for 48 weeks. One noncirrhotic patient with HCV genotype 1b infection and CKD stage 5 relapsed 12 weeks after the end of treatment. SVR12 was

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
100 mg/50 mg once daily for 12 weeks) vs **Intensive pharmacokinetic group** Elbasvir/grazoprevir 100 mg/50 mg once daily for 12 weeks	ribavirin only, CKD with GFR ≤29 (including those on hemodialysis)	12 weeks		achieved in all six patients with cirrhosis. Secondary: Not reported
Lawitz et al.[53] (2015) C-WORTHY Elbasvir/grazoprevir 100 mg/50 mg once daily for 12 weeks plus weight-based ribavirin vs elbasvir/grazoprevir 100 mg/50 mg once daily for 12 weeks vs elbasvir/grazoprevir 100 mg/50 mg once daily for 18 weeks plus weight-based ribavirin vs elbasvir/grazoprevir 100 mg/50 mg once daily for 18 weeks	MC, OL, PG, R Patients >18 years of age with chronic HCV genotype 1 infection with baseline HCV-RNA levels ≥10,000 IU/mL who were treatment-naïve with compensated cirrhosis (cohort 1) or were null responders to prior peginterferon plus ribavirin with or without compensated cirrhosis (cohort 2)	N=253 12 to 16 weeks	Primary: SVR12 Secondary: Not reported	Primary: Among patients in cohort 1 receiving ribavirin, 90.3% (28/31) and 96.9% (31/32) achieved SVR12 in 12-week and 18-week groups, respectively. Among patients in cohort 1 not receiving ribavirin, 96.6% (28/29) and 93.5% (29/31) achieved SVR12 in 12-week and 18-week groups, respectively. Among patients in cohort 2 receiving ribavirin, 93.8% (30/32) and 100% (33/33) achieved SVR12 in 12-week and 18-week groups, respectively. Among patients in cohort 2 not receiving ribavirin, 90.9% (30/33) and 96.9% (31/32) achieved SVR12 in 12-week and 18-week groups, respectively. Among patients in cohort 2 without cirrhosis, SVR12 was achieved in 92.5% (37/40) of patients with 12 weeks of treatment and 97.6% (41/42) with 18 weeks, respectively. Among patients in cohort 2 who had cirrhosis, SVR12 was achieved in 92.0% (23/25) of patients with 12 weeks of treatment and 100% (23/23) with 18 weeks, respectively. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Kwo et al.[54] (2017) SURVEYOR-1 Part 1 and 2 and SURVEYOR-2 Part 1 and 2 **Part 1: dose-ranging study** Glecaprevir 200 mg plus pibrentasvir 120 mg once daily for 12 weeks (Groups A, D, G) vs glecaprevir 200 mg plus pibrentasvir 40 mg once daily for 12 weeks (Groups B and I) vs glecaprevir 300 mg plus pibrentasvir 120 mg once daily for 12 weeks (Group C and F) vs glecaprevir 200 mg plus pibrentasvir 120 mg and weight-based ribavirin once daily for 12 weeks (Groups E and H) **Part 2** glecaprevir 300 mg plus pibrentasvir 120 mg once daily for eight weeks (Group K, L, and M) or 12 weeks (Groups N and O)	OL, MC, RCT Patients 18 to 70 years of age with chronic HCV genotype 1 (Groups A, B, K), 2 (Groups C, D, E, L), 3 (Groups F-I, M [TN], N [TE]), 4, 5, or 6 (all Group O) with HCV RNA >10,000 IU/mL without cirrhosis who were treatment-naïve or failed prior treatment with peginterferon alfa and ribavirin Enrolled patients were not previously treated with regimens containing DAAs.	N=449 Eight or 12 weeks	Primary: SVR12 Secondary: SVR4, on-treatment virologic failure, and relapse	Primary: **Part 1: dose-ranging study** In patients with HCV genotype 1, the SVR12 rates were 100% (40/40; 95% CI, 91 to 100%) and 97% (38/39; 95% CI, 87 to 100%) in Groups A and B, respectively. In patients with HCV genotype 2, the SVR12 rates were 96% (24/25; 95% CI, 80 to 99%), 100% (24/24; 95% CI, 86 to 100%), and 100% (25/25; 95% CI, 87 to 100%) in Group C, D, and E, respectively. In patients with HCV genotype 3, the SVR12 rates were 93% (28/30; 95% CI, 79 to 98%), 93% (28/30; 95% CI, 79 to 98%), 93% (28/30; 95% CI, 79 to 98%), and 83% (25/30; 95% CI, 66 to 93%) in Groups F, G, H, and I, respectively. **Part 2** The SVR12 rates were 97% (33/34; 95% CI, 85 to 99%) in patients with genotype 1, 98% (53/54; 95% CI, 90 to 100%) in patients with genotype 2, 97% (28/29; 95% CI, 83 to 99%) in treatment-naive patients with genotype 3, 92% (22/24; 95% CI, 74 to 98%) in treatment-experienced patients with genotype 3, and 100% (34/34; 95% CI, 90 to 100%) in patients with genotype 4, 5, and 6 (Groups K, L, M, N, and O, respectively. Secondary: Rates of SVR4 were not reported. **Part 1: dose-ranging study** There were no virologic failures in Groups A, C, D, E, K, L, M, and O. Three patients had a virologic breakthrough (Groups H, I, N; one in each group). Seven patients had a relapse following treatment completion (one in Groups B, F, and N and two in Groups G and I). Three patients had missing data (Groups F, I, M; one in each group). Five patients discontinued treatment early (Groups C, H, I, K, L; one in each group).
Gane et al.[55] (2016)	OL, RCT (SURVEYOR-	**SURVEYOR-1 Part 2**	Primary: SVR12	Primary: **SURVEYOR-1 Part 2**

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
SURVEYOR-1 Part 2 and SURVEYOR-2 Part 2 **SURVEYOR-1 Part 2** Glecaprevir 200 mg plus pibrentasvir 120 mg once daily for 12 weeks (Group A) **SURVEYOR-2 Part 2** Glecaprevir 300 mg plus pibrentasvir 120 mg and ribavirin 800 mg once daily for 12 weeks (Group B) vs glecaprevir 300 mg plus pibrentasvir 120 mg once daily for 12 weeks (Group C)	2 Part 2 only) Patients 18 to 70 years of age with chronic HCV genotype 1 (SURVEYOR-1 Part 2) or genotype 3 (SURVEYOR-2 Part 2) with compensated cirrhosis who were treatment-naïve or failed prior treatment with peginterferon alfa and ribavirin Enrolled patients were not previously treated with regimens containing DAAs.	N=27 12 weeks **SURVEYOR-2 Part 2** N=55 16 weeks (N=4, all TE from Group B) 12 weeks (N=51, Groups B and C)	Secondary: SVR4, on-treatment virologic failure, and relapse	Among patients with genotype 1 treated with glecaprevir 200 mg plus pibrentasvir 120 mg, the SVR12 rate was 96% (26/27; 95% CI, 82 to 99). **SURVEYOR-2 Part 2** Among patients with genotype 3 treated with glecaprevir 300 mg plus pibrentasvir 120 mg and ribavirin, the SVR12 rate was 100% (27/27; 95% CI, 88 to 100). Among patients with genotype 3 treated with glecaprevir 300 mg plus pibrentasvir 120 mg, the SVR12 rate was 96% (27/28; 95% CI, 82 to 99). Secondary: **SURVEYOR-1 Part 2** Rates of SVR4 were not reported. Of 27 patients, one treatment-naive patient with genotype 1a infection relapsed at post-treatment week four. **SURVEYOR-2 Part 2** Rates of SVR4 were not reported. Of 55 patients, one treatment-experienced patient with genotype 3 infection who received 16-week treatment relapsed at post-treatment week two.
Hézode et al.[56] (2015) PEARL-I Ombitasvir 25 mg plus paritaprevir 150 mg plus ritonavir 100 mg once daily with or without weight-based ribavirin	MC, OL, R Patients 18 to 70 years of age with non-cirrhotic, chronic HCV genotype 4	N=135 12 weeks	Primary: SVR12 Secondary: Post treatment relapse, on-treatment virological	Primary: In treatment-naive patients, SVR12 rates were 100% in the ribavirin-containing regimen and 90.9% in the ribavirin-free regimen; there was no statistical difference in SVR12 rates between these two treatment groups after adjusting for interleukin 28B genotype (mean difference −9.16%, 95% CI −19.61 to 1.29; P=0.086). All treatment-experienced patients in the ribavirin-containing group achieved SVR12.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
for 12 weeks	infection who were treatment-naïve or and treatment-experienced (prior interferon alfa with or without ribavirin) with baseline HCV-RNA levels ≥10,000 IU/mL		failure, SVR4, and rapid virological response	Secondary: Rates of rapid virological response and SVR4 were similar or numerically higher in treatment-naive patients who received the ribavirin-containing regimen compared with those who did not receive ribavirin. No relapses between post treatment week 12 and post treatment week 24 have been recorded in treatment-naive patients in either treatment group; the treatment-experienced patients have not yet reached post treatment week 24, but no relapses have been observed after post treatment week 12 in this group of patients.
Asselah et al.[57] (2016) AGATE-I Ombitasvir 25 mg plus paritaprevir 150 mg plus ritonavir 100 mg once daily with or without weight-based ribavirin for 12 or 16 weeks	MC, OL, R Treatment-naive and interferon or pegylated interferon and ribavirin treatment-experienced patients ≥18 years of age with HCV genotype 4 infection and compensated cirrhosis	N=120 48 weeks post-treatment	Primary: SVR12 Secondary: Virologic failure, adverse events	Primary: SVR12 was achieved in 97% patients randomly allocated to receive 12 weeks of treatment and in 98% of patients allocated to receive 16 weeks of treatment. For both treatment groups, superiority to the predefined threshold was shown because the lower bounds of the CIs for the proportion of patients with SVR12 were higher than 67%, the threshold based on pegylated interferon and ribavirin treatment for HCV genotype 4 infection. Secondary: One patient in the 12-week group experienced virological breakthrough and one discontinued prematurely after the first day of treatment. One patient missed the post-treatment week 12 visit in the 16-week group. Adverse events in more than 10% of all patients were asthenia (18% in the 12-week group; 32% in the 16-week group), fatigue (17% in the 12-week group; 33% in the 16-week group), headache (23% in the 12-week group; 23% in the 16-week group), anaemia (15% in the 12-week group; 20% in the 16-week group), pruritus (8% in the 12-week group; 23% in the 16-week group), nausea (10% in the 12-week group; 13% in the 16-week group), and dizziness (7% in the 12-week group; 15% in the 16-week group).
Waked et al.[58] (2016) AGATE II	OL, partly randomized Patients ≥18	N=160 12 or 24 weeks	Primary: SVR12 Secondary:	Primary: SVR12 was achieved in 94 of 100 (94%) of patients in the group without cirrhosis. In the cirrhosis 12-week treatment group, 30 (97%; 95% CI, 84 to 99)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ombitasvir 25 mg plus paritaprevir 150 mg plus ritonavir 100 mg once daily with or without weight-based ribavirin for 12 (patients without cirrhosis) or for either 12 or 24 weeks (patients with compensated cirrhosis were randomly assigned to a treatment duration)	years of age chronically infected with HCV genotype 4 who were HCV treatment-naive or treatment-experienced with interferon-based regimens		On-treatment virological failure and with posttreatment relapse within 12 weeks of the end of treatment	of 31 achieved SVR12; one patient did not suppress HCV RNA to less than the lower limit of quantification by treatment week six and discontinued treatment. In the cirrhosis 24-week treatment group, SVR12 was achieved in 27 (93%; CI, 78 to 98) of 29 patients. Secondary: Four patients in the group without cirrhosis experienced virological failure (one on-treatment rebound and three relapses), one patient discontinued treatment prematurely (withdrawn consent), and one patient died on post-treatment day 17 for reasons deemed unrelated to study drugs. One of the patients who experienced relapse in the without cirrhosis group had F4 compensated cirrhosis at baseline. In the cirrhosis 24-week treatment group, one patient had on-treatment virological breakthrough and one patient was lost to follow-up after achieving an SVR at post-treatment week four.
Feld et al.[59] (2015) ASTRAL-1 Sofosbuvir 400 mg/ velpatasvir 100 mg once daily for 12 weeks vs placebo	DB, MC, PC, R Patients >18 years of age with chronic HCV genotype 1, 2, 4, 5 or 6	N=706 12 weeks	Primary: SVR12 Secondary: Not reported	Primary: Overall, SVR12 rate in the sofosbuvir/velpatasvir group of 99% (618/624; 95% CI, 98 to >99) was higher than the prespecified benchmark rate of 85% (P<0.001). None of the 116 patients in the placebo group achieved SVR12. In the sofosbuvir/velpatasvir group, SVR12 rates were 98% (206/210; 95% CI, 95 to >99) in patients with genotype 1a infection, 99% (117/118; 95% CI, 95 to 100) with genotype 1b, 100% (104/104; 95% CI, 97 to 100) with genotype 2, 100% (116/116; 95% CI, 97 to 100) with genotype 4, 97% (34/35; 95% CI, 85 to >99) with genotype 5, and 100% (41/41; 95% CI, 91 to 100) with genotype 6. Of 121 patients in the sofosbuvir/velpatasvir group with any genotype who had cirrhosis, 120 (99%; 95% CI, 95 to >99) achieved SVR12. Of 201 treatment-experienced patients in the sofosbuvir/ velpatasvir group, 200 (>99%) achieved SVR12; all 56 patients who previously failed a regimen containing an HCV protease inhibitor, peginterferon alfa, and ribavirin achieved SVR12. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Foster et al.[60] (2015) ASTRAL-2 and ASTRAL-3 Sofosbuvir 400 mg/ velpatasvir 100 mg once daily for 12 weeks vs sofosbuvir 400 mg for 12 weeks (HCV genotype 2) or 24 weeks (HCV genotype 3) and ribavirin (1,000 mg/day if weight <75 kg or 1,200 mg/day if weight ≥75 kg) twice daily for 12 weeks (HCV genotype 2) or 24 weeks (HCV genotype 3)	AC, MC, OL, R Patients >18 years of age with chronic HCV genotype 2 (ASTRAL-2) or HCV genotype 3 (ASTRAL-3)	N=266 (ASTRAL-2) N=552 (ASTRAL-3) 12 to 24 weeks	Primary: SVR12‡ Secondary: Not reported	Primary: **ASTRAL-2** Among patients with HCV genotype 2, the overall SVR12 rate in the 12-week sofosbuvir/velpatasvir group was 99% (133/134; 95% CI, 96 to 100) as compared to 94% (124/132; 95% CI, 88 to 97) in the 12-week sofosbuvir/ribavirin (difference, 5.2; 95% CI, 0.2 to 10.3; P=0.02). **ASTRAL-3** Among patients with HCV genotype 3, the overall SVR12 rate in the 12-week sofosbuvir/velpatasvir group was 95% (264/277; 95% CI, 92 to 98) as compared to 80% (221/275; 95% CI, 75 to 85) in the 24-week sofosbuvir/ribavirin group (difference, 14.8; 95% CI, 9.6 to 20.0; P<0.001). In the 12-week sofosbuvir/velpatasvir group and 24-week sofosbuvir/ribavirin group, respectively, the SVR12 rates were 98% (160/163) and 90% (141/156) in treatment-naïve patients without cirrhosis, 93% (40/43) and 73% (33/45) in treatment-naïve patients with cirrhosis, 91% (31/34) and 71% (22/31) in treatment-experienced patients without cirrhosis, and 89% (33/37) and 58% (22/38) in treatment-experienced patients with cirrhosis. In the 12-week sofosbuvir/velpatasvir group, SVR12 rates were higher (97%; 225/231) in patients without baseline NS5A RAVs as compared to those with baseline NS5A RAVs (88%; 38/43). The absence of Y93H NS5A RAV at baseline was associated with higher SVR12 (97% [42/249] vs 84% [21/25]). Secondary: Not reported
Gane et al.[61] (2013) Group 1: Sofosbuvir 400 mg and ribavirin 1,000 mg/day (weight	OL Patients19 years of age or older, who had	N=95	Primary: Serum HCV RNA levels, safety	Primary: Viral suppression was rapid in all patients, regardless of genotype, status with respect to previous treatment, baseline viral load, race or ethnic group, IL28B status, and presence or absence of interferon in the regimen. All 95 patients had an undetectable level of HCV RNA

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<75 kg) or 1,200 mg/day (weight ≥75 kg) for 12 weeks Group 2: Group 1 treatment plus 4 weeks of concomitant peginterferon alfa-2a 180 µg once weekly Group 3: Group 1 treatment plus 8 weeks of concomitant peginterferon alfa-2a 180 µg once weekly Group 4: Group 1 treatment plus 8 weeks of concomitant peginterferon alfa-2a 180 µg once weekly (additional groups amended): Group 5: Sofosbuvir 400 mg daily monotherapy for 12 weeks Group 6: Sofosbuvir plus peginterferon and ribavirin for 8 weeks	chronic HCV infection without cirrhosis		Secondary: Not reported	by week four, with viral suppression sustained through the end of treatment. All 40 patients with HCV genotype 2 or 3 infection who received sofosbuvir and ribavirin for 12 weeks had an undetectable level of serum HCV RNA at two, four, eight, 12, 24, and 48 weeks after treatment. The presence or absence of peginterferon alfa-2a appeared to have no effect on viral kinetics or rate of sustained virologic response. Six of the 10 patients in the sofosbuvir monotherapy group had a sustained virologic response at 12 and 24 weeks after treatment. All 95 patients completed treatment. The most common adverse events were headache, fatigue, insomnia, nausea, rash, and anemia. Hematologic abnormalities were more common among patients who received interferon than among those who did not. Neutropenia and thrombocytopenia were not observed in the groups that did not receive interferon. However, sofosbuvir monotherapy was associated with a modest decrease in the hemoglobin level. Secondary: Not reported
Molina et al.[62] (2015) PHOTON-2 Once-daily sofosbuvir 400 mg plus twice-daily ribavirin (1000 mg in patients with bodyweights <75 kg and 1200 mg in those with weights ≥75 kg) was given for 24 weeks to all patients except treatment-naïve patients with	MC, non-randomized, OL, uncontrolled Patients (aged ≥18 years) co-infected with stable HIV and chronic HCV genotypes 1–4,	N=274 12 or 24 weeks	Primary: SVR12 Secondary: Not reported	Primary: Overall rates of SVR12 were 85% (95% CI, 77 to 91) in patients with genotype-1 HCV, 88% (69 to 98) in patients with genotype-2 HCV, 89% (81 to 94) in patients with genotype-3 HCV, and 84% (66 to 95) in patients with genotype-4. Response rates in treatment-naïve patients with HCV genotypes 2 or 3 (89% [95% CI, 67 to 99] and 91% [81 to 97], respectively) were similar to those in treatment-experienced patients infected with those genotypes (83% [36 to 100] and 86% [73 to 94], respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
genotype-2 HCV, who received a 12-week regimen	including those with compensated cirrhosis			Secondary: Not reported
Jacobson et al.[63] (2013) POSITRON and FUSION POSITRON: Sofosbuvir 400 mg once daily for 12 weeks and ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) for 12 weeks vs placebo FUSION: Sofosbuvir 400 mg once daily for 12 weeks and ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight of ≥75 kg) for 12 weeks vs sofosbuvir 400 mg once daily for 16 weeks and ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight of ≥75 kg) for 16 weeks	POSITRON: DB, MC, PC, R Patients ≥18 years of age with confirmed diagnosis of chronic HCV infection (genotypes 2 or 3), serum HCV RNA levels of ≥10,000 IU/mL during screening, and who are not candidates for interferon therapy FUSION: AC, DB, MC, R Patients ≥18 years of age with confirmed diagnosis of chronic HCV infection (genotypes 2 or 3), serum HCV RNA levels of	POSITRON: N=278 12 weeks FUSION: N=201 12 to 16 weeks	POSITRON: Primary: SVR12 Secondary: Not reported FUSION: Primary: SVR12 Secondary: Not reported	POSITRON: Primary: Treatment with sofosbuvir plus ribavirin achieved a SVR12 in 78% of patients (95% CI, 72 to 83) compared to 0% among those receiving placebo (P<0.001). Response rates in patients receiving sofosbuvir plus ribavirin were lower among patients with genotype 3 infection than among those with genotype 2 infection (61 vs 93%). Among patients with genotype 3 infection receiving sofosbuvir plus ribavirin, 21% of patients with cirrhosis achieved a SVR12 compared to 68% without cirrhosis. Among patients with genotype 2 infection receiving sofosbuvir plus ribavirin, 94% of patients with cirrhosis achieved a SVR12 compared to 92% without cirrhosis. Secondary: Not reported FUSION: Primary: Treatment with sofosbuvir plus ribavirin resulted in higher rates of SVR12 in the 12-week group (50%; 95% CI, 40 to 60) and 16-week group (73%; 95% CI, 63 to 81) compared to historical control rate of 25%. Patients receiving 16 weeks of treatment had a significantly higher rate of SVR than patients receiving 12 weeks of treatment (difference, -23%; 95% CI, -35 to -11; P<0.001). Response rates in patients with genotype 2 infection who received 12

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	≥10,000 IU/mL during screening, and who have previously not responded to treatment with an interferon containing regimen			weeks of treatment were lower than among those who received 16 weeks of treatment (86 vs 94%; difference of -8%; 95% CI, -24 to 9); however, the difference was not statistically significant. Response rates in patients with genotype 3 infection who received 12 weeks of treatment were significantly lower than among those who received 16 weeks of treatment (difference, -32%; 95% CI, -48 to -15). Among patients with cirrhosis who received 12 weeks of treatment, the rate of response was 31% (60% with HCV genotype 2 infection and 19% with HCV genotype 3 infection), as compared to 61% among patients without cirrhosis (96% with HCV genotype 2 infection and 37% with HCV genotype 3 infection). Among patients with cirrhosis who received 16 weeks of treatment, the rate of response was 66% (78% with HCV genotype 2 infection and 61% with HCV genotype 3 infection) as compared to 76% among patients without cirrhosis (100% with HCV genotype 2 infection and 63% with HCV genotype 3 infection). Secondary: Not reported
Zeuzem et al.[64] (2014) VALENCE Sofosbuvir 400 mg once daily for 12 weeks and ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) for 12 weeks vs placebo	DB, MC, PC, R Patients ≥18 years of age with confirmed diagnosis of chronic HCV infection (genotypes 2 or 3) and serum HCV RNA levels of ≥10,000 IU/mL	N=419 12 weeks (genotype 2) or 24 weeks (genotype 3)	Primary: SVR12 Secondary: Not reported	Primary: Treatment with sofosbuvir plus ribavirin achieved a SVR12 in 93% (95% CI, 85 to 98) of patients with HCV genotype 2 receiving 12 weeks of therapy and 85% (95% CI, 80 to 89) of patients with HCV genotype 3 receiving 24 weeks of therapy. Among patients with genotype 2 infection receiving sofosbuvir plus ribavirin, high SVR12 rates were observed in treatment-naïve non-cirrhotics (96.7%; 95% CI, 82.8 to 99.9), treatment-naïve cirrhotics (100%; 95% CI, 15.8 to 100), and treatment-experienced non-cirrhotics (93.8%; 95% CI, 79.2 to 99.2), whereas lower SVR12 rate was observed in treatment-experienced cirrhotics with genotype 2 infection (77.8%; 40.0 to 97.2).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
After study initiation, on the basis of emerging data from phase 3 trials, the study was unblinded, treatment for all patients with genotype 3 infection was extended to 24 weeks, the placebo group was terminated, and the goals of the study were redefined to be descriptive and not include hypothesis testing.	during screening			Similarly, among patients with genotype 3 infection receiving sofosbuvir plus ribavirin, high SVR12 rates were observed in treatment-naïve non-cirrhotics (94.6%; 95% CI, 86.3 to 97.6), treatment-naïve cirrhotics (92.3%; 95% CI, 64.0 to 99.8), and treatment-experienced non-cirrhotics (86.7%; 95% CI, 78.4 to 92.7), whereas lower SVR12 rate was observed in treatment-experienced cirrhotics with genotype 3 infection (61.7%; 46.4 to 75.5). Secondary: Not reported
Lawitz et al.[65] (2014) COSMOS Group 1: simeprevir and sofosbuvir with ribavirin for 24 weeks vs Group 2: simeprevir and sofosbuvir without ribavirin for 24 weeks vs Group 3: simeprevir and sofosbuvir with o ribavirin for 12 weeks vs Group 4: simeprevir and sofosbuvir without ribavirin for 12 weeks	OL, RCT Patients ≥18 years of age with chronic HCV genotype 1 infections who had previously not responded to pegylated interferon and ribavirin or were treatment naïve	N=167 12 or 24 weeks	Primary: SVR12 Secondary: SVR4, SVR24, on-treatment failure, viral relapse	Primary: 154 (92%) of 167 of patients achieved SVR12, 90% (95% CI, 81 to 96) in cohort 1 and 94% (87 to 98) in cohort 2. SVR12 was seen in 98 (91%) of 108 patients who received ribavirin vs 56 (95%) of 59 of those who did not. Rates were similar by treatment status (38 [95%] of 40 treatment-naive patients vs 116 [91%] of 127 previous non-responders) or treatment duration (77 [94%] of 82 after 12 weeks of treatment vs 77 [91%] of 85 after 24 weeks). Secondary: All patients who achieved SVR12 also achieved SVR4. More than 91% of patients overall achieved SVR4. Rapid virological response was achieved in 81% of patients overall, but SVR12 was still achieved in all but one who had detectable HCV RNA titers four weeks after the start of treatment. No patients experienced on-treatment virological failure, including viral breakthrough. Six patients had viral relapse after the end of treatment. At the time of relapse, five of the six had developed resistance-associated mutations to simeprevir, but none to sofosbuvir.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
[Cohort 1: previous non-responders to peginterferon and ribavirin with moderate liver fibrosis (METAVIR score F0–F2); Cohort 2: previous non-responders to peginterferon and ribavirin or treatment naïve with severe liver fibrosis (METAVIR score F3–F4)]				
Jacobson et al.[66] (2017) POLARIS-2 and POLARIS-3 Sofosbuvir 400 mg/velpatasvir 100 mg/voxilaprevir 100 mg once daily for 8 weeks vs sofosbuvir 400 mg/velpatasvir 100 mg once daily for 12 weeks	OL, MC, R (GT 1 through 4 only) Patients >18 years of age with chronic HCV genotype 1,2,4,5, or 6 with or without compensated cirrhosis or chronic HCV genotype 3 without cirrhosis (POLARIS-2) or chronic HCV genotype 3 with compensated cirrhosis (POLARIS-3) Enrolled patients were not previously treated with regimens	**POLARIS-2** N=943 Eight or 12 weeks **POLARIS-3** N=220 Eight or 12 weeks	Primary: SVR12 Secondary: HCV RNA kinetics, viral resistance	Primary: **POLARIS-2** The overall SVR12 rate was 95% (95% CI, 93 to 97) in the sofosbuvir/velpatasvir/voxilaprevir group and 98% (95% CI, 96 to 99) in the sofosbuvir/velpatasvir group, with a difference of -3.4% (95% CI, -6.2 to -0.6). Since the lower bound of the 95% CI for the difference was below -5%, the prespecified criteria for non-inferiority were not met. In the sofosbuvir/velpatasvir/voxilaprevir group, SVR12 rates were 92% (155/169) in patients with genotype 1a infection, 97% (61/63) with genotype 1b, 97% (61/63) with genotype 2, 99% (91/92) with genotype 3, 94% (59/63) with genotype 4, 94% (17/18) with genotype 5, and 100% (30/30) with genotype 6. In the sofosbuvir/velpatasvir group, SVR12 rates were 99% (170/172) in patients with genotype 1a infection, 97% (57/59) with genotype 1b, 100% (53/53) with genotype 2, 97% (86/89) with genotype 3, 98% (56/57) with genotype 4, and 100% (9/9) with genotype 6. Among patients without cirrhosis, SVR12 rates were 96% (395/411) in sofosbuvir/velpatasvir/voxilaprevir group and 98% (349/356) in sofosbuvir/velpatasvir group. Corresponding SVR12 rates in patients with cirrhosis were 91% (82/90) and 99% (83/84), respectively. **POLARIS-3** The overall SVR12 rate was 96% (95% CI, 91% to 99%) in both treatment groups, which was significantly greater than the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	containing DAAs.			performance goal of 83% (P<0.001 for both groups). Secondary: **POLARIS-2** Of 498 patients receiving sofosbuvir/velpatasvir/voxilaprevir, 250 had viral variants associated with resistance to NS3 and/or NS5A inhibitors at baseline. The SVR12 rates for patients with and without baseline resistance were 94% and 98%, respectively. For patients with genotype 1a, SVR12 rates in patients with and without baseline resistance were 89% and 95%, respectively. Baseline Q80K resistance-associated substitution, the most commonly observed NS3 variant, was associated with a reduction in SVR12 rate for genotype 1a patients receiving sofosbuvir/velpatasvir/voxilaprevir (88 vs 94%). Of the 21 patients who relapsed in the sofosbuvir/velpatasvir/voxilaprevir group by post-treatment week 12, one had treatment-emergent NS5A resistance-associated substitutions Q30R and L31M. Among patients receiving sofosbuvir/velpatasvir, one of the three patients who relapsed had treatment-emergent Y93N variant, which is associated with resistance to NS5A inhibitors, at relapse. **POLARIS-3** All 46 patients with baseline resistance (23 from each treatment group) achieved a SVR12. Neither of the two patients who relapsed after treatment with sofosbuvir/velpatasvir/voxilaprevir had treatment-emergent resistance, whereas both patients with virologic failure in the sofosbuvir/velpatasvir group had the Y93H variant, which is associated with resistance to NS5A inhibitors, at time of virologic failure.

Study abbreviations: AC=active control, CI=confidence interval, DB=double-blind, MA=meta-analysis, MC=multicenter, NI=non-inferiority, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, R=randomized, RCT=randomized controlled trial, RR=relative risk, SG=single group
Other abbreviations: ALT=alanine aminotransferase, ART=antiretroviral therapy, DAA=direct-acting antiviral, CKD=chronic kidney disease, GFR=glomerular filtration rate, HCV=hepatitis C virus, HIV=human immunodeficiency virus, IU=international units, PEG=peginterferon, RAV=resistance associated variants, RNA=ribonucleic acid, SVR=sustained virologic response, TE=treatment-experienced, TN=treatment-naïve.

Additional Evidence

Dose Simplification
Kowdley et al compared SVR24 between 12- and 24-week treatment courses with sofosbuvir, finding no difference in the proportion of patients achieving SVR24 between cohorts A (12 weeks) and B (24 weeks) (P=0.94) or between cohorts A (12 weeks) and C (24 weeks) (P=0.78), suggesting no additional benefit of treatment durations longer than 12 weeks.[30]

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 21. Relative Cost of the HCV Antivirals

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Daclatasvir	tablet	Daklinza®	$$$$$	N/A
Simeprevir	capsule	Olysio®	$$$$$	N/A
Sofosbuvir	tablet	Sovaldi®	$$$$$	N/A
Combination Products				
Dasabuvir Sodium, Ombitasvir, Paritaprevir, and Ritonavir	dose pack, extended release tablet	Viekira Pak®, Viekira XR®	$$$$$	N/A
Elbasvir and grazoprevir	tablet	Zepatier®	$$$$$	N/A
Glecaprevir and pibrentasvir	tablet	Mavyret®	$$$$$	N/A
Ledipasvir and sofosbuvir	tablet	Harvoni®	$$$$$	N/A
Ombitasvir, paritaprevir, and ritonavir	tablet	Technivie®	$$$$$	N/A
Sofosbuvir and velpatasvir	tablet	Epclusa®	$$$$$	N/A

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Sofosbuvir, velpatas, and voxilaprev	tablet	Vosevi®	$$$$$	N/A

N/A=Not available

X. Conclusions

The hepatitis C virus (HCV) antiviral agents are Food and Drug Administration (FDA)-approved for the treatment of chronic hepatitis C virus (HCV) infection. These agents act via several different mechanisms of action, including inhibition of non-structural (NS) 3/4A protease, NS5B polymerase, and HCV NS5A.[15,16]

The goal of hepatitis C treatment is HCV eradication, which is predicted by the achievement of sustained virologic response (SVR), defined as the absence of HCV RNA 12 weeks following treatment discontinuation. Many factors need to be considered when initiating HCV treatment, including both patient specific (e.g., response to prior treatment, presence of cirrhosis) as well as HCV specific (e.g., viral genotype and subtype, baseline viral load, baseline resistance to DAAs).[12-14]

Prior to the availability of HCV antivirals, combination of peginterferon and ribavirin has been the standard of care for the treatment of chronic hepatitis C. Treatment guidelines developed by the American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) do not currently include recommendations for the newest agents, Mavyret® and Vosevi®. In general, combination regimens that include newer HCV antivirals are preferred over older peginterferon-based regimens due to a higher SVR rate, improved side effects profile, and reduced pill burden. However, recommended regimens may occasionally include ribavirin to improve SVR rates in certain difficult to treat populations (e.g., based on HCV genotype, prior treatment history, presence of cirrhosis, or when used in certain special populations).[13] The guidelines also state that although regimens of sofosbuvir and ribavirin or pegylated interferon/ribavirin plus sofosbuvir, simeprevir, telaprevir, or boceprevir are FDA-approved for particular genotypes, they are inferior to the current recommended regimens. The interferon-containing regimens are associated with higher rates of serious adverse events (e.g., anemia and rash), longer treatment duration in some cases, high pill burden, numerous drug-drug interactions, more frequent dosing, and higher intensity of monitoring for safety or treatment response.[13]

Olysio® (simeprevir) is a once-daily, oral HCV NS3/4A protease inhibitor Food and Drug Administration (FDA)-approved for the treatment of HCV genotype 1 infection (in combination sofosbuvir or peginterferon alfa and ribavirin) and in the treatment of HCV genotype 4 infection (in combination with peginterferon alfa and ribavirin). Its use is not recommended in patients with HCV genotype 1a containing the Q80K polymorphism, moderate or severe hepatic impairment, or prior failure of HCV protease inhibitor-containing regimens.[2] The consensus guidelines from the AASLD)/IDSA recommend against the use of simeprevir plus peginterferon and ribavirin given the availability of all-oral regimens with improved tolerability and efficacy.[13] Incivek® (telaprevir) and Victrelis® (boceprevir) have been discontinued in the United States in October 2014 and December 2015, respectively.

Sovaldi® (sofosbuvir) is a once-daily, oral HCV nucleotide analog NS5B polymerase inhibitor, FDA-approved for the treatment of HCV genotype 1, 2, 3 or 4 infection, including those with hepatocellular carcinoma (HCC) awaiting liver transplantation and those with HCV/HIV co-infection. It is indicated for use in combination with peginterferon alfa and ribavirin in the treatment of HCV genotype 1 and 4 and in combination with ribavirin alone in the treatment of HCV genotype 2 and 3 infection, and in patients with HCC awaiting liver transplant. Use in combination with ribavirin alone can be considered in patients with chronic HCV genotype 1 infection who are not candidates for an interferon-based regimen.[3]

Daklinza® (daclatasvir) is a once-daily NS5A inhibitor FDA-approved for use in combination with Sovaldi® (sofosbuvir) for 12 weeks in HCV genotype 1 and 3 infection.[1] The AASLD/IDSA guidelines recommend extending treatment duration to 24 weeks in cirrhotic patients and also adding ribavirin in treatment-experienced cirrhotics only with HCV genotype 3 infection. The AASLD/IDSA guidelines also support use in HCV genotype 2, decompensated cirrhosis, and post liver transplant.[13]

Epclusa® (sofosbuvir/velpatasvir) is a once-daily combination of sofosbuvir, an HCV NS5B polymerase inhibitor, and velpatasvir, an HCV NS5A inhibitor that is indicated for the treatment of chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection in adults. The FDA-approved treatment duration is 12 weeks regardless of the presence or absence of cirrhosis. The addition of ribavirin is recommended in patients with decompensated cirrhosis and in select patients with HCV genotype 3 infection.[10]

Harvoni® (ledipasvir/sofosbuvir) is a once-daily combination of ledipasvir, an HCV NS5A inhibitor, and sofosbuvir, an HCV NS5B polymerase inhibitor. Harvoni® (ledipasvir/sofosbuvir) is indicated for the treatment of chronic HCV genotype 1, 4, 5, and 6 infection in adults.[8] Sovaldi® (sofosbuvir) and Harvoni® (ledipasvir/sofosbuvir) are now also indicated for the treatment of HCV in pediatric patients 12 years of age and older or weighing ≥35 kg with genotype 1, 4, 5, or 6 (Harvoni®) and genotype 2 or 3 (Sovaldi®) without cirrhosis or with compensated cirrhosis.[3,8]

Viekira Pak® (ombitasvir/paritaprevir/ritonavir/dasabuvir), with or without ribavirin, is indicated for the treatment of patients with chronic HCV genotype 1 infection. It includes ombitasvir, an HCV NS5A inhibitor, paritaprevir, an HCV NS3/4A protease inhibitor, ritonavir, a CYP3A inhibitor, and dasabuvir, an HCV non-nucleoside NS5B palm polymerase inhibitor. The FDA-approved treatment duration is 12 or 24 weeks depending on prior treatment history and cirrhosis status. Viekira® is not recommended for use in patients previously treated with an HCV protease inhibitor or in patients who have decompensated liver disease. Co-administration of Viekira® with drugs that are highly dependent on CYP3A for clearance, strong inducers of CYP3A and CYP2C8, and strong inhibitors of CYP2C8 is contraindicated. Viekira XR® (dasabuvir/ombitasvir/paritaprevir/ritonavir extended-release) is a fixed-dose, once-daily combination tablet formulation.[4-5]

Technivie® (ombitasvir/paritaprevir/ritonavir) is a fixed-dose combination of ombitasvir, an HCV NS5A inhibitor, paritaprevir, an HCV NS3/4A protease inhibitor, and ritonavir, a CYP3A inhibitor. It is FDA-approved in combination with ribavirin for 12 weeks in the treatment of patients with chronic HCV genotype 4 infection who do not have cirrhosis. Administration without ribavirin may be considered in treatment-naïve patients with contraindication or intolerance to ribavirin.[9]

Zepatier® (elbasvir/grazoprevir) is a once-daily combination tablet containing the NS5A inhibitor elbasvir and the NS3/4A protease inhibitor grazoprevir that is indicated with or without ribavirin for treatment of chronic HCV genotypes 1 or 4 infection in adults. The approved regimen (with or without ribavirin) and treatment duration (12 or 16 weeks) vary based on HCV genotype, prior treatment history, and for patients HCV with genotype 1a infection, the presence of certain NS5A polymorphisms at baseline.[6]

Mavyret® (glecaprevir/pibrentasvir) is a once-daily combination product FDA-approved for the treatment of chronic HCV infection in adults with genotype 1 through 6 without cirrhosis or with compensated cirrhosis, including patients with moderate to severe renal impairment or human immunodeficiency virus (HIV)-coinfection. It is also approved for adults with HCV genotype 1 who have been previously treated with an HCV NS5A inhibitor or an NS3/4A protease inhibitor, but not both. It is the first treatment of eight weeks duration approved for all HCV genotypes.[7] Mavyret® is not recommended for patients with decompensated cirrhosis.[7] Mavyret® contains two novel drugs: glecaprevir, an NS3/4A PI, and pibrentasvir, an HCV NS5A inhibitor. Both drugs interfere with the enzymes required for viral replication.[7]

Vosevi® (sofosbuvir/velpatasvir/voxilaprevir) is a once-daily combination product FDA-approved for the treatment of chronic HCV infection in adults with genotype 1 through 6 without cirrhosis or with compensated cirrhosis. It is the first treatment approved for patients who have been previously treated with a direct-acting antiviral (DAA) regimen containing Sovaldi® (sofosbuvir) or NS5A inhibitor. The safety and efficacy has not been established in patients with severe renal impairment, decompensated cirrhosis, or post-liver transplant.[11] Vosevi® contains two previously approved drugs: sofosbuvir, an HCV nucleotide analog NS5B polymerase inhibitor, and velpatasvir, an HCV NS5A inhibitor. It also contains a new drug, voxilaprevir, an NS3/4A protease inhibitor. Vosevi® is approved for 12 weeks only as a salvage therapy for patients who have failed a DAA regimen.[11] In contrast, Mavyret® (glecaprevir/pibrentasvir) has been approved for a broad population of patients, including DAA-naïve and DAA-experienced.[7]

Zepatier®, Harvoni®, Viekira®, Olysio® plus Sovaldi®, Epclusa®, and Daklinza® plus Sovaldi® are all recommended treatment options for genotype 1 treatment-naïve patients without cirrhosis in the AASLD/IDSA

guidelines. Mavyret® and Vosevi® have not yet been incorporated into the guidelines. In general, the guideline recommendations are in line with FDA-approved indications, and the HCV antivirals in various combinations, with or without ribavirin, are the preferred treatment regimens. Treatment regimens with direct-acting agents or combinations, which may or may not also include ribavirin, are recommended based on HCV genotype, previous treatment experience, presence of cirrhosis, and certain special populations.[13] Overall, data from clinical trials support the FDA-approved indications and dosing recommendations for these agents.[1-11] The trials demonstrate that treatment with HCV antiviral agents result in a significant improvement in SVR when compared to historical response rates or placebo. Direct-acting antivirals have not been directly compared in clinical trials.[17-66]

There is insufficient evidence to support that one brand HCV antiviral is safer or more efficacious than another. The drugs in this AHFS class are used in a specific patient population. Because these agents have narrow indications with limited usage, and very specific criteria must be met prior to initiating therapy, these agents should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand HCV antivirals 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 HCV antiviral 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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